

Ludwig Zirngibl

Antifungal Azoles

A Comprehensive Survey
of their Structures and Properties



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1 Introduction

Scope, chronology and statistics, beneficial side effects, acknowledgements.

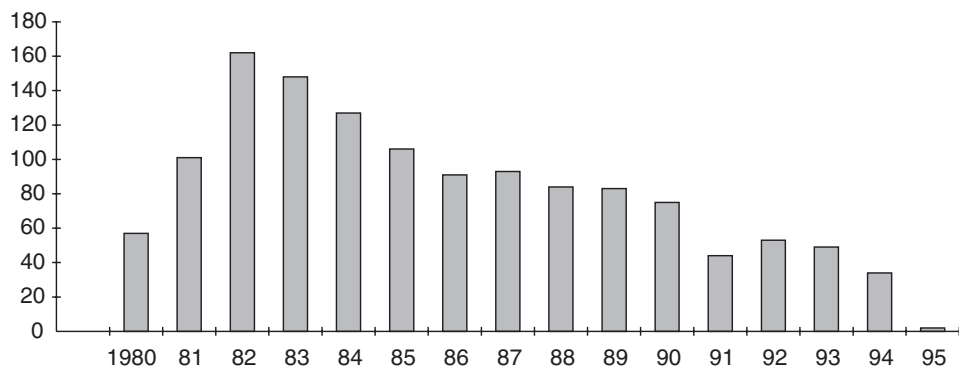


Fig. 1.1 Chronology of 1309 patent applications of antifungal azoles, chapters 2 to 7, up to 30 June 1996; see also appendix.

Almost 15 years ago a forerunner of this book presented the first 15 years of research on antifungal azoles, first discovered in 1965.[1.01] The results of 575 patent applications and 225 papers had been presented based strictly on organic chemistry structures.

That review seems to have been useful for organizing, executing and interpreting the search for new antifungal azoles. So with his retirement from Siegfried, the author sought the advice of leading authorities (see Acknowledgements), to determine in what scope a successor review might be planned for the second 15-year period in the face of an increase by a factor of 2.3 in the number of patents (see Table 1.1). In this situation the author was happy to find that Wiley-VCH were interested in publishing the review in book form and particularly pleased that, after the first trial chapters were ready, Siegfried also expressed a wish to further the work.

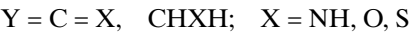
Structural arrangement follows closely the earlier paper, [1.01] yet with finer subdivisions to make orientation easier. A complete coverage of the patent literature has been attempted up to 30 June, 1996, using original documents, Chemical Abstracts (CA) and Derwent. For the benefit of academic library users, the majority of Derwent abstracts have been converted into CA references. Within the chapters, patents of the same family have been identified by identical application number *and* application date and thus a second citation could be avoided. Yet, double citation and therefore slight positive errors in the statistics of patents

Table 1.1 Number of first applications by pharmaceutical companies

1978—1995 ^{d)}	(1965—1980) ^{a) c)}	Company ^{b)}
282	(185)	Bayer
107	(40)	BASF
89	(36)	Sumitomo
44	(6)	Ciba-Geigy
42	(3)	Pfizer
38	(1)	Kureha
36	(30)	ICI
34	(9)	Hoechst
33	(30)	Janssen
23	(3)	Schering Corp.
21	(1)	Hokko
18		Nihon Nohyaku
16		Rohm and Haas
15 each		DuPont, Shionogi
14		Pennwalt
13		Rhone-Poulenc, Kyowa
12		Sandoz
11		Sankyo
10		Takeda
9 each		Schering AG, Montedison, Morishita
8 each		Inke, Mitsubishi, Ube, Uniroyal, Uriach
7 each		Bristol-Myers, Otsuka, Syntex, Toyama
6 each		Celamerck, Lentia, Meiji, Mitsui, SDS, SS Pharmaceuticals
5 each		Hodogaya, Hoffmann-LaRoche, Kao, Nippon, Koyaku, Siegfried
1—4 each		>150 ^{e)} individuals, companies and institutes

a) From [1.01], p. 261.
b) If the patent applicant consists of a group of companies, only the first named is cited.
c) The majority of applications (189) for 1978 and 1979 are cited in [1.01], the minority (24) is included here.
d) The majority of applications (57) for 1980 is cited in this table, the minority (15) has been included in [1.01].
e) Only 27 for 1965—1980.[1.01]

still might occur caused by extreme patent claims or by ‘partly continuation of now abandoned’ applications. Indeed, frightening umbrella claims in title markush formulas such as



would formally require entrance into six chapters or sections of this book. Here the compound with the most interesting activity has been used to place the information

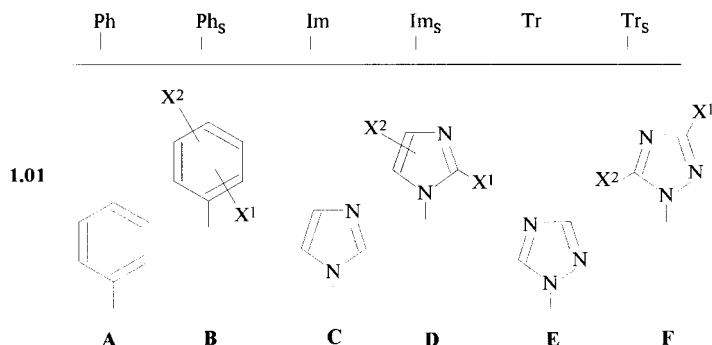


Fig. 1.2 Abbreviations of carbocyclic and heterocyclic structures

into context, and if deemed necessary, cross references have been added for one or more chapters for the other claims.

Only the first three authors of patents or papers have been used in the literature list to keep reference writing within bounds. General structural formulas ('title formulas') are further condensed by abbreviations **1.01A** to **F**.

Az stands for Im or Tr, and in rare cases (specified) for other 1-substituted monocyclic 1H-azoles. Azole substituents are restricted to 'hydrocarbyl' (alkyl, alkenyl, aryl, arylalkyl etc.)

Substituents of markush formulas are given as examples only. This also holds for names of individual commercial or experimental antifungals, and for licensees; no completeness of such information can be expected there.

In contrast to the earlier review,[1.01] 1-acylazoles and metalorganic antifungal azoles are included.

The following classes of compounds are not treated: Azoles with functional substituents, such as nitroimidazoles; bicyclic azoles such as benzimidazoles; mixtures, synergism and combination therapy.

Papers on mode of action, molecular pharmacology, biochemistry and those of mainly medical interest have received only marginal treatment.

Commercial agents are treated in this book, in comparison to their citation list (see Tables 1.2 and 1.3) relatively less than experimental agents.

It is hoped that the latter can be compared with structurally related drugs. The top five to seven substances in these tables are characterized by double use as drugs and as research standards, and show very high citation rates. Imazalil (486 citations) has not been included since it is used in a triple function: As a veterinary antimycotic, as an agricultural fungicide and also as a standard.

Right from the beginning, medicinal chemistry work in this field has been of particular fascination because applications are possible in two fields, medicine and agriculture. Quantitatively, research on antifungal azoles reached its peak in the first half of the 1980s (see Fig. 1.1), resulting in a number of successful antimycotics for topical and vaginal application, and in fungicides which control diseases of many crops—from seed treatment to protection of the shipment boxes.

Table 1.2 Citation frequency of azole antimycotics 1968–1996^{a)}

Rank	Name	CA citations
01	ketoconazole	1135
02	clotrimazole	804
03	miconazole	772
04	fluconazole	554
05	itraconazole	345
06	econazole	293
07	bifonazole	157
08	tioconazole	131
09	isoconazole	53
10	sulconazole	44
11	oxiconazole	42
12	terconazole	41
13	lanconazole	34
14	sertaconazole	33
15	croconazole	33
16	fenticonazole	24
17	butoconazole	22
18	neticonazole	21
19	omoconazole	15
20	flutrimazole	14

a) Limit 30.06.1996.

By the end of the 1980s the desire to find better antimycotics for oral treatment, of low toxicity for lifelong prophylaxis and of low tendency to develop resistance for the treatment of immunocompromized patients, has been felt more and more pressing. The high cost and the disappointments of this research can be seen from the number of firms which phased down their research commitment or stopped it altogether.

Dozens of reviews per year have been reported by CA on different aspects of antifungal azoles and antifungal therapy in general. The reader is addressed to the following outstanding and recent papers and books on the medicinal chemistry aspects,[1.02, 1.03, 1.04, 1.05, 1.06] medical requirements,[1.07, 1.08, 1.09, 1.10] modes of action and resistance,[1.11, 1.12, 1.13, 1.14] and problems of self-medication of antimycotics.[1.15] Important fungicide reviews cover medicinal chemistry aspects, [1.16, 1.17] and modes of action.[1.18, 1.19]

A recent call to examine at the beneficial side effects of our class of drugs is shown in Table 1.4.[1.20]

Even the notorious capacity of antifungals to produce resistant strains has been turned into an advantage.

Acknowledgements. The author is grateful for the advice in the planning stage of the book to Prof. Karl Heinz Büchel, Bayer; Prof. José Elguero, Madrid; Dr. Vasil St. Georgiev, NIH Bethesda; Dr. S. Jolidon, Hofmann-La Roche Basel and Prof. Manfred Köller, Cornell University.

Table 1.3 Citation frequency of azole fungicides 1968–1996^{a)}

Rank	Name	CA citations
01	triadimefon	1393
02	propiconazole	737
03	triadimenol	676
04	prochloraz	564
05	bitertanol	446
06	flusilazole	229
07	penconazole	187
08	flutriafol	165
09	myclobutanil	154
10	fenapanil	130
11	diclobutrazole	129
12	hexaconazole	121
13	cyproconazole	117
14	triflumizole-(<i>E</i>)	116
15	CGA 169374	66
16	difenoconazole	66
17	fluotrimazole	59
18	te(r)buconazole	52
19	fenbuconazole	32
20	tetraconazole	28
21	epoxiconazole	28
22	imibenconazole	28
23	bromuconazole	27
24	diniconazole	27
25	metconazole	25
26	triticonazole	19
27	fluquinconazole	8
28	SSF 109	7
29	furconazole cis	7

a) Limit 30.06.1997.

During the writing, the author enjoyed continuous guidance by Dr. T. Kellersohn and Dr. Annette Eckerle of Wiley-VCH. Dr. Barbara Brandau-Krug of VCH, Mr. N. Kansy and Mrs. Corinna Michel of Siegfried never lost patience when problems arose in connection with the writing and drawing process. I am indebted to Dr. Hans-Ruedi Marti of Siegfried for a permit to use the company library at my convenience and for on-line searches.

By reading my manuscript, Dr. S. Jolidon, Hoffmann-La Roche, Mr. P. Rieblly and Dr. W. Kunz of Novartis, and Dr. J. Heeres from Janssen/C.M.D. Beerse, contributed their intimate knowledge of the field—contributions for which I am particularly grateful.

A great number of medicinal chemists helped by sending reprints, and my former colleagues and coworkers at Siegfried never passed by without a word of interest or encouragement.

Last but not least I thank my wife Barbara for her patience with a husband who was around in the house but often quite far away with his mind.

Table 1.4 Beneficial side effects of antifungal azoles

activity, use against	examples of agents
a) activities of established antifungal azoles:	
anticancer	clotrimazole, ketoconazole
antidiarrheal	clotrimazole
anti-inflammatory	croconazole, flutrimazole
antiperspirant	miconazole
antiprotozoal (Chagas disease, leishmaniasis)	ketoconazole, D080
antisporeulant	imazalil
antithyroid	ketoconazole
antiviral (herpes)	clotrimazole
cyclosporin reduction	ketoconazole
enzyme catalyst improvement	clotrimazole, uniconazole, propiconazole
sickle cell anemia	clotrimazole
b) side effects developed into experimental or commercial, non-antifungal azole drugs:	
anticancer	arimidex, erbulozole, liarozole, tubulozole
ascaricide	azacyclotin
herbicide	metazachlor
hypolipidemic	azalanstat
plant growth regulator	triapenthenol, uniconazole, BAS 111.W, LAB 117682, LAB 130827, ZT 112449
c) further activities seen in antifungal azole series:	
algicide, anticorrosion,	
antiarrhythmic, antistatic,	
aromatase inhibition, lysomotropic,	
picornavirus inhibition,	
radioprotective, spermicide	

2 1-(Hydrogen-, alkyl-, aryl-, heterocyclyl-, arylalkyl-, heterocyclylalkyl-, diphenylalkyl and trityl)1-H-azoles

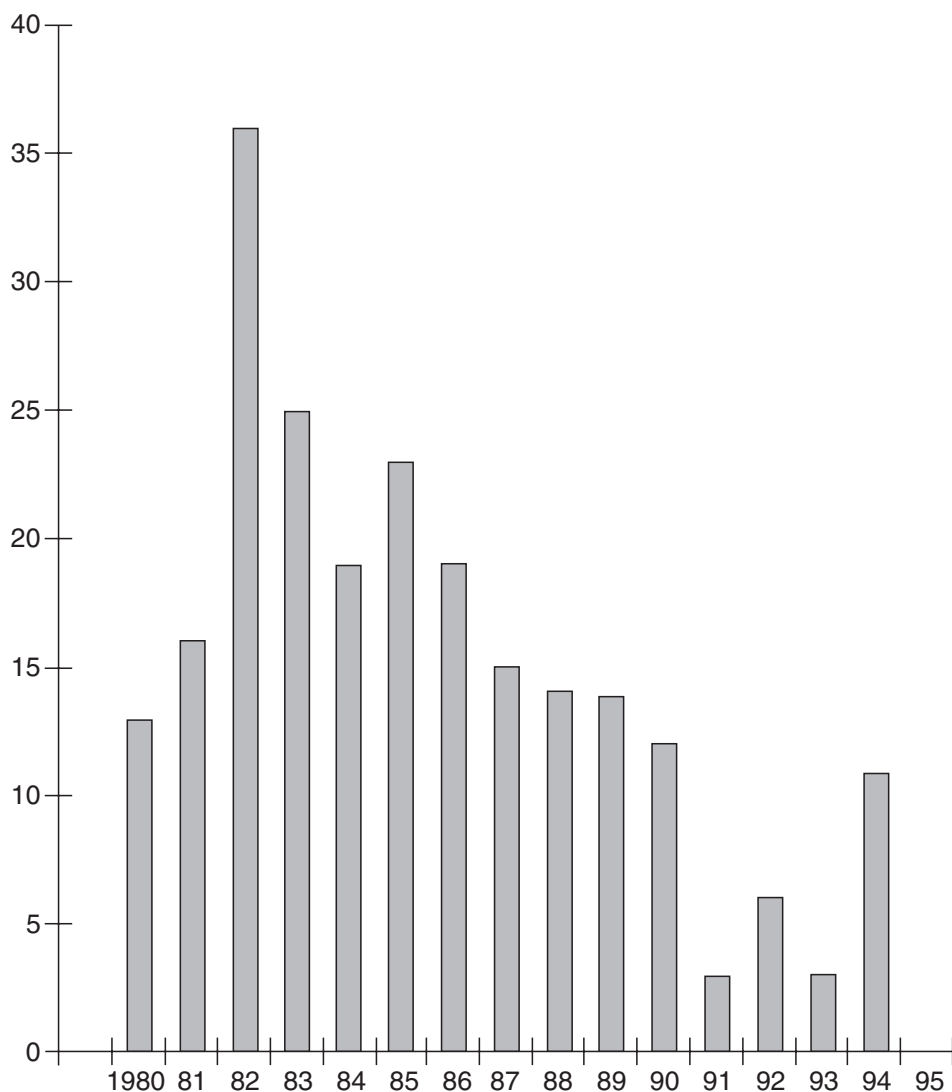


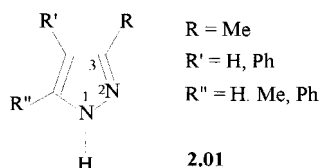
Fig. 2.1 Chronology of 187 patent applications for Chapter 2.

2.1 1-Hydrogen- and 1-alkyl-azoles

2.1.1 Pyrroles and pyrazoles

For 1-alkylation of pyrroles and pyrazoles, see recent reviews.[2.001, 2.002] Pyrazoles and other azoles can be alkylated with alcohols under pressure.[2.003]

Unsubstituted pyrazole shows no antimicrobial activity, but 3-, 4- and/or 5-alkyl or phenylpyrazoles **2.01** inhibit *Aspergillus niger*,[2.004] and *Staphylococcus aureus*. [2.005]

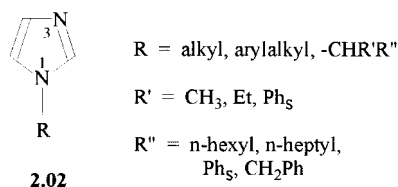


Copper-II-complexes of 3,5-dimethylpyrazole have similar activities.[2.006]

3-Phenylpyrazoles with H or various acid groups at N¹ protect plants from fungal diseases.[2.007]

2.1.2 Imidazoles

Preparative methods for 1-alkylimidazoles **2.02** have been reviewed,[2.008, 2.009] and new variants have been introduced.[2.010]



With alkyl halides and aqueous sodium hydroxide as reagents,[2.011] addition of 1–20% product increases the yield.[2.012] Other catalysts include KF on alumina in acetonitrile,[2.013] imidazole sodium on alumina,[2.014] phase transfer catalysis (PTC) with TBAB or in polyethylene glycol,[2.010, 2.015, 2.016] and γ - Al_2O_3 and H-Y zeolites.[2.017, 2.018] A new route starts from 1-alkyl-3-(2-cyanoethyl)imidazolium compounds and removes the cyanoethyl group with base at room temperature.[2.008]

1-Octylimidazole can be used as crystallization inhibitor for fungicide sprays.[2.019]

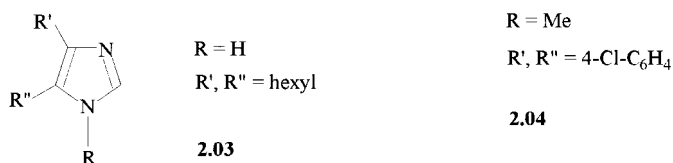
1-(2-Nonyl)imidazole has been proposed as biocide against *Penicillium brevicaulis*, *Chaetomium globosum* and *Aspergillus niger*. [2.020]

(For antifungal 14-imidazolylmethyl-lanosterol, see section 6.1.2).

Chiral 1-alkylimidazoles **2.02** with e.g. $R = \text{CH}(\text{CH}_3)\text{C}_6\text{H}_{13}$ can be prepared from the corresponding 4,5-dicyanoimidazoles in two steps. [2.021, 2.022]

1,4-Disubstituted imidazoles are synthesized from α -bromoketones by reaction with primary amines followed by cyclization. [2.023]

4,5-Disubstituted 1H-imidazoles such as the 4,5-dihexyl derivative **2.03** have been claimed as topical, parenteral and oral antimycotics with fewer side effects than established drugs. [2.024]

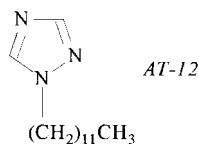


Another highly active compound **2.04** of this series inhibits *Bacillus subtilis*, *Staph. aureus* and *Piricularia oryzae*. [2.025]

Similar compounds are part of a larger claim. [2.026]

In a series of higher 1-alkylimidazoles **2.02**, minimum inhibitory concentrations (MICs) for a number of microorganisms have been correlated with optimal chain lengths (see Table 2.1 and Fig. 2.2). [2.027] Mixtures of similar quaternary compounds with phosphonobutane-tricarboxylic acid show a synergistic effect on bactericidal and anti-mould activities. [2.028]

1-Dodecylimidazole **2.05**, AT-12 [4303-67-7] exerts a lysomotropic effect like other weakly basic amines. It becomes highly concentrated in the lysosomes of mammalian cells leading to their disruption. [2.030, 2.031]



The agent inhibits *Bacillus megaterium*, and a great number of filamentous fungi and yeasts including *Saccharomyces cerevisiae*. [2.029] It also has strongly lipid-lowering effects. [2.172]

1-Dodecyl-2-methylimidazole presents high activity against *Trichophyton rubrum*. [2.032, 2.033]

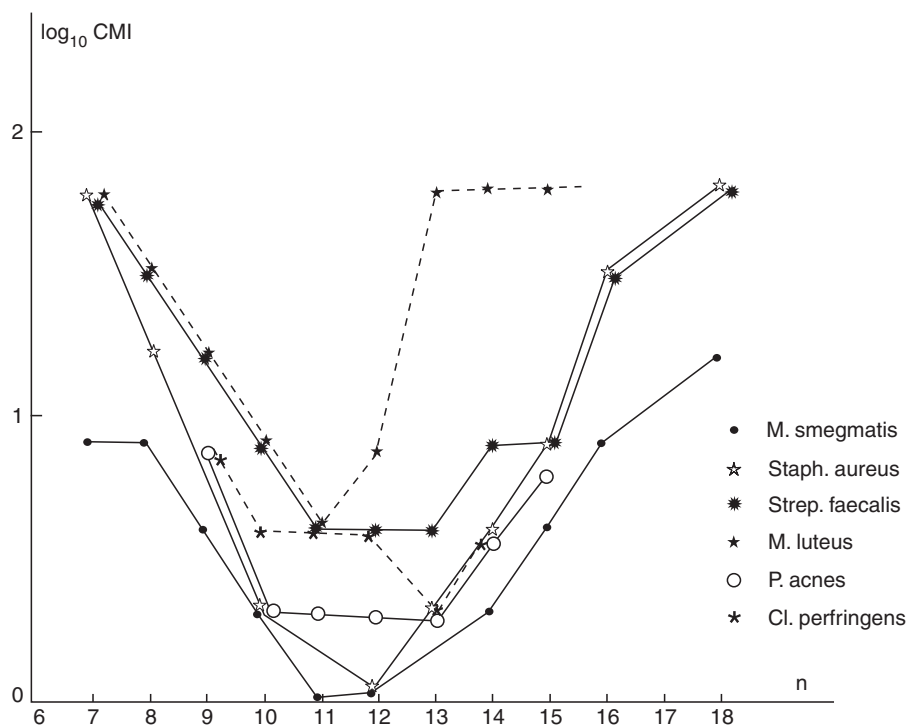


Fig. 2.2 Variation of minimal inhibition concentrations of *M. smegmatis*, and Gram-positive bacteria, versus number of carbon atoms *n* of the alkyl chain.[2.027]

Similar quaternized compounds have been claimed as fungicides and algicides.[2.034, 2.035]

Sorbic acid salts of antibacterial and antifungal 1-alkyl and 1-arylimidazoles have been recommended as preservatives for pharmaceuticals, food and other materials.[2.036]

2.1.3 Azoles

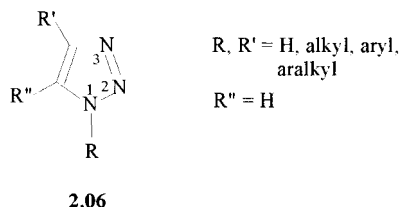
Bis-azolyalkanes can be prepared from azoles and dihaloalkanes under PTC catalysis.[2.037] Azolyl- and azolylmethyl-cycloalkanes have been part of larger claims for fungicides and plant growth regulators.[2.038, 2.039, 2.040]

Table 2.1 Minimal inhibition concentrations (µg/ml) as a function of n, the length of alkyl group. For refs. (*numbers in italics*), see. [2.027]

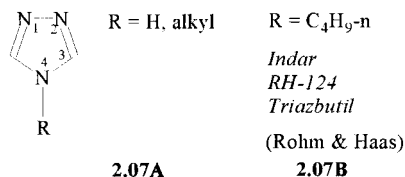
Microorganism	7	8	8	9	10	11	12	13	14	15	16	18	Metronidazole	Ketoconazole	Clotrimazole
<i>M. smegmatis</i>	8	8	4	2	1	1	1	2	2	4	8	16			
Gram-positive aerobic bacteria															
<i>Staph. aureus</i>	64	16	8	2	2	1	1	2	4	8	32	64	>256 (41)		
<i>S. faecalis</i>	64	32	16	8	4	4	4	(31.2) (25)	8	8	32	64	>256 (41)		
<i>M. luteus</i>	64	32	16	8	4	8	64	64	64	64	>128	>128			
Gram-negative aerobic bacteria															
<i>P. aeruginosa</i>	>128	>128	>128	>128	128	128	128	32	32	16	32	64			
<i>E. coli</i>	128	64	32	32	32	64	(>1000) (25)	>128	>128	>128	>128	>128	>256 (41)		
							(>1000) (25)						>128 (42)		
Gram-positive anaerobic bacteria															
<i>P. acnes</i>	>12.8	>12.8	8	2	2	2	2	2	4	8	>12.8	>12.8	>128 (43)		
<i>Cl. perfringens</i>	>12.8	>12.8	8	4	4	4	4	2	4	>12.8	>12.8	>12.8	0.5 (41)		
													0.25 (42)		
Gram-negative anaerobic bacteria															
<i>Vibrio</i> sp.	>128	>128	>128	128	64	32	32	64	128	>128	>128	>128	0.27 (44)		
Yeasts															
<i>P. ovalis</i>	>128	32	16	4	4	8	8	8	32	64	>128	>128	0.01-0.05 (45)		
<i>C. albicans</i>	>512	>512	256	128	128	32	32	(15.6) (25)	64	128	>512	>512	<0.07 (46)		7,4 (47)
Dermatophytes															
<i>M. canis</i>	>128	>128	>128	128	16	16	16	>128	>128	>128	>128	>128	<0.01 (48)		

2.1.4 Triazoles

1-Alkyl-1,2,3-triazoles **2.06** are prepared from alkyl halides as reviewed,[2.041] or from their 5-thiols by reductive desulfurization with Raney-Ni catalyst and hydrazine hydrate.[2.042]



1-Alkylation of 1,2,4-triazoles is achieved using sodium methylate as base.[2.043] or under PTC,[2.044, 2.045] and has been reviewed recently. [2.044, 2.045] 4-Substituted by-products **2.07A** are suppressed through thermodynamic control.[2.048]



A new one-pot regiospecific synthesis starts from 4-amino-1,2,4-triazole which on alkylation yields 1-alkyl-4-amino-1,2,4-triazole. The amino group is then eliminated with sodium nitrite.[2.049]

Higher 1-alkyl-1,2,4-triazole hydrobromides are claimed to inhibit corrosion of metals by sulfate-reducing bacteria.[2.050, 2.051]

Triazbutil **2.07B** [16227-10-4], now superseded, presented a rare example of a 4-alkylated 4H-1,2,4-triazole. It was introduced 1970 as agricultural fungicide against *Puccinia recondita* f. sp. tritici of cereals.[2.052, 2.053, 2.054]

Goitropic effects have been observed in mammals. [2.055]

1-Alkyl-5-diarylmethyl-1,2,4-triazoles control *Erysiphe cichoracearum* on cucumber seedlings.[2.056]

2.1.5 Tetrazoles

1-Alkylation of the title compounds is achieved through 2-tert. butyltetrazoles,[2.057] which has been briefly reviewed.[2.058]

2.2 1-Aryl-1H-azoles

2.2.1 Pyrazoles

1-Arylation can be effected starting from activated fluorobenzenes.[2.059] Another reagent is aryllead triacetate.[2.060]

1-(2-Hydroxyphenyl)-pyrroles are potent inhibitors of *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*. [2.061]

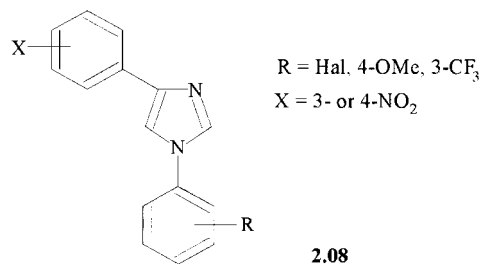
1-(x-Nitrophenyl)-3- or -5-phenylpyrazoles inhibit *Staph. aureus*. [2.062].

2.2.2 Imidazoles

1-Arylation of imidazole can also be achieved with activated fluorobenzenes,[2.063, see also 2.009] or with aryllead triacetates.[2.060]

1-Phenylimidazole hydrochloride is devoid of antibacterial activity.[2.064]

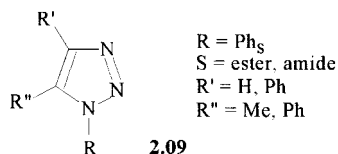
1-Carboxyalkylphenyl-imidazole-3-oxides have antiviral activities.[2.065] 1,4-Diphenyl-imidazoles **2.08** show activity against a large number of *Candida albicans* strains.[2.066, 2.067]



1-(4-Methoxyphenyl)-4-(4-nitrophenyl)imidazole has high activity against a number of *Candida albicans* strains and Gram-negative bacteria.[2.068]

2.2.3 1,2,3-Triazoles

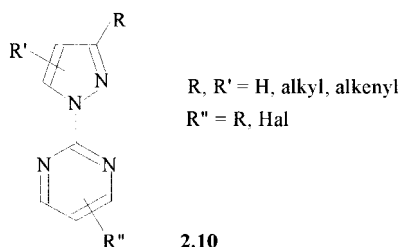
Compounds **2.09** have been recommended as agricultural bactericides.[2.069, 2.070]



2.3 1-Heteroaryl-1H-azoles

2.3.1 Pyrazoles

2-(1-Pyrazol-1-yl)pyrimidines **2.10** show promise as microbicides due to their activity against *Piricularia oryzae*, *Pellicularia sasakii* and *Helminthosporium oryzae* on rice.[2.071]



Some 1-(3-pyrazol-1-yl)indazoles display antibacterial and antifungal activities.[2.072] (Pyrazol-1-yl)quinolines inhibit growth of *Salmonella typhi* and *Escherichia coli*. [2.073]

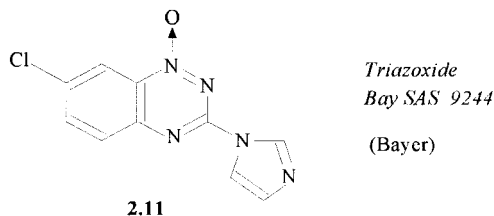
2.3.2 Imidazoles

1-(3-Pyrazol-1-yl)imidazoles show no antimicrobial activity.[2.074]

3-(1H-Imidazol-1-yl)pyridazines,[2.075] and similar -pyridazinones,[2.076] have been claimed as antimycotics.

7-(1H-Imidazol-1-yl-4-oxo-quinoline-carboxylic acids have been described as bactericides.[2.077]

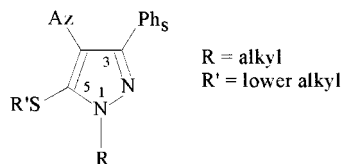
Triazoxide, **2.11** [72459-58-6] is used for the control of *Helminthosporum* spp. on seeds.[2.078]



3-(1H-Imidazol-1-yl)-2,3-dihydrobenzopyranones [2.079] and 8-(1H-Imidazol-1-yl)-benzo[ij]quinolizine-2-carboxylic acids have been claimed as bactericides. [2.080]

2.3.3 Azoles and triazoles

4-(1H-Azol-1-yl)-4-pyrazoles **2.12** control *Botrytis cinerea* infection on zinnia seedlings, and show plant growth regulatory activities as well.[2.081, 2.082]



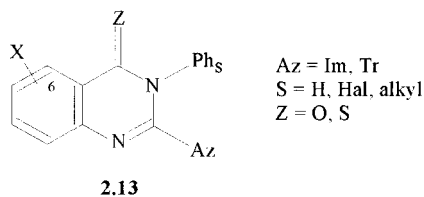
2-(1H-Azol-1-yl)pyrrolidinones are active against *Erysiphe cichoracearum*. [2.083]
 x-(1H-1,2,4-triazol-1-yl)-isoxazoles and -pyrimidines are active as plant growth regulators. [2.084]

A number of x-(1H-azol-1-yl) bicyclic heterocycles, such as isoquinolin-1-ones control powdery mildew on barley.[2.085]

(1H-1,2,4-Triazol-1-yl)-quinolines inhibit *Erysiphe graminis* and powdery mildew on barley.[2.086, 2.087]

4-(1H-Azol-1-yl)-2-phenyl-quinazolines are toxic to bacteria, filamentous fungi and HeLa cells. [2.088]

Fungicidal and plant growth-regulating 2-(Azol-1-yl)quinazolinones **2.13** have been disclosed.[2.089]



Az = Im, Tr
 S = H, Hal, alkyl
 Z = O, S

Ph _S = 2,4-Cl ₂ C ₆ H ₃	2,4-Cl ₂ C ₆ H ₃
Z = O	O
Az = Tr	Tr
X = H	6-F
quinconazole	fluquinconazole
SN 539 865	SN 597 265
(Schering Corp.)	(AgrEvo)

A

B

Their development has resulted in quinconazole **2.13A** and fluquinconazole **2.13B**.

Quinconazole **2.13A** [103970-75-8] has been developed as a fungicide.[2.090] Its toxicity against plant pathogenic fungi is generally lower than that of prochloraz with the exception of *Ustilago maydis*. [2.091, 2.092] Its environmental fate has been elucidated.[2.093]

Fluquinconazole **2.13B** [136426-54-5] controls *Venturia inaequalis* and *Podosphaera leucotricha* in apple, *Uncinula necator* in vines, *Puccinia* spp. and *Septoria* spp. on wheat, *Cercospora*, *Erysiphe* on sugar beet, and other fungal pathogens on coffee, turf, legumes, on rice and stone fruit.[2.094, 2.095, 2.096]

(1H-Triazolyl-1-methyl)-cyclopenta[b]furan derivatives inhibit *Erysiphe graminis* f. sp. *tritici* on wheat seedlings.[2.097]

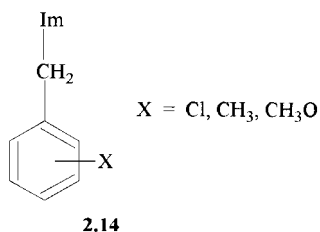
2.4 1-Benzyl-1H-azoles

2.4.1 Pyrazoles

1,1'-Methylenedipyrazoles inhibit anaerobic protozoa such as *Trichomonas* and *Entamoeba*. [2.098, 2.099]

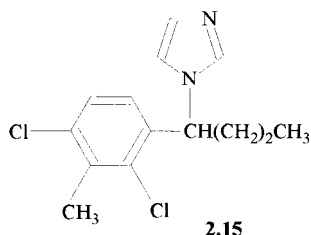
2.4.2 Imidazoles

1-Benzylimidazoles **2.14** can be prepared from benzyl halides and imidazole under alkaline conditions,[2.099, 2.100] or from 3-acetyl or 3-benzoyl-imidazoles and benzyl halides followed by deprotection of the acyl group in water or alcohol.[2.101]

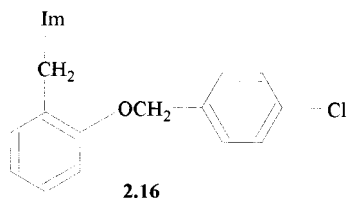


Chiral α -alkyl-1-benzylimidazoles may be prepared from the corresponding 4,5-dicyanoimidazoles. [2.021, 2.022]

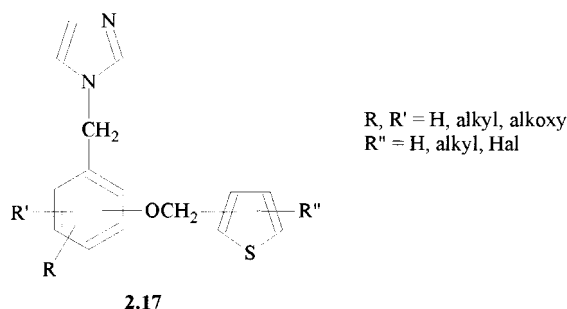
While 1-benzylimidazole is devoid of antibacterial activity,[2.064] an α -butyl homolog **2.15** [138995-29-6], shows activity against *Pythium graminicola*, *Fusarium oxysporum* and *Rhizoctonia solani*. [2.102, 2.103, 2.104, 2.105]



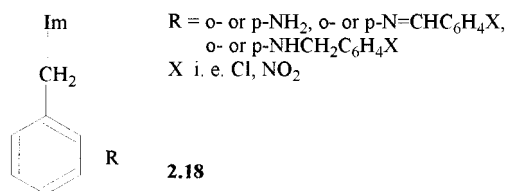
Another 1-benzylimidazole **2.16**, with an antimicrobial potency like clotrimazole served as a lead structure for the development of croconazole (see section 2.9.2).[2.106]



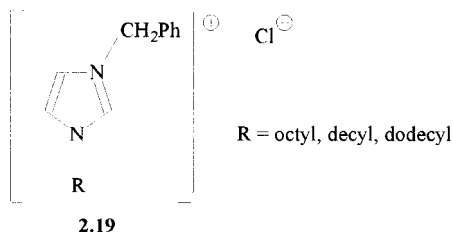
Related structures include compounds **2.17** with good activities against *Streptococcus faecalis*, *Trichophyton mentagrophytes*, *Aspergillus niger*, *Candida albicans* and *Microsporum lanosum*. [2.107]



In a series of 1-(x-benzylamino- and benzylidenamino)benzyl-imidazoles **2.18**, the nitro-substituent has proved optimal for activity against a large number of *Candida* strains. [2.108, 2.109]



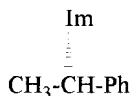
Quaternary higher 1-alkyl-3-benzylimidazolium chlorides **2.19** show activity against *Staphylococcus* and *E. coli* increasing with chain length, but decreasing against *Pseudomonas*. [2.110]



In this series, inhibition of *Trichophyton mentagrophytes* and *Microsporum lanosum* has been found independent of chain length. [2.110] In a similar group of

antibacterial imidazolium salts, positions 2, 4 and 5 of the imidazole ring have been substituted with alkyl or aryl.[2.111]

Enantiomerically pure (S)-(+)-1-(1-phenylethyl)imidazole **2.20** is prepared from the corresponding (S)- α -alkylbenzylamine,[2.021] or from 4,5-dicyanoimidazole.[2.022]

**2.20**

2.4.3 Azoles

Imidazole and triazole can be benzylated using PTC,[2.112] or with NaH in 1,2-dimethoxyethane, and further mono- or dibenzylated in the α -position.[2.180] Many 1-alkylation procedures cited earlier are also useful for benzylations.[2.008, 2.010, 2.015, 2.044, 2.045, 2.101, 2.102] Benzyl chlorides carrying substituents at the phenyl ring react with pyrazole, imidazole, and 1,2,4-triazole to yield the corresponding 1-substituted azoles.[2.113] Photostimulation of 4-nitrobenzyl chloride results in similar products in a classical $S_{\text{RN}}1$ -reaction. [2.114]

2.4.4 Triazoles

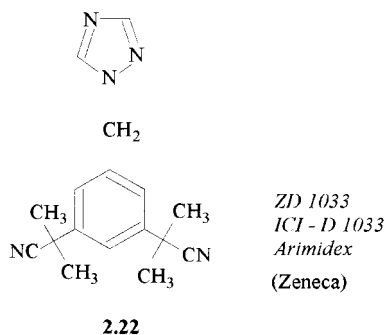
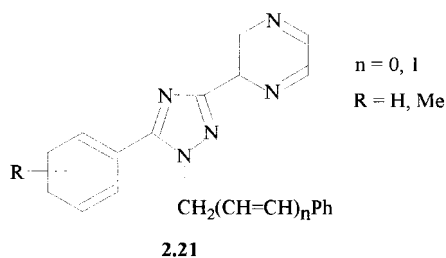
1-Benzyl-1,2,3-triazoles can be prepared from benzyl azides and acetylene under pressure.[2.115, 2.116] [1-(1H-1,2,4-triazol-1-yl)ethyl]benzene is obtained by base-catalyzed dephosphorylation of the addition product from triazole and $\text{Ph-CH=CHP(O)(OH)}_2$.[2.117] Asymmetrically 3,5-disubstituted 4H-1,2,4-triazoles can be prepared from 1,3,4-oxadiazoles and benzylamine. [2.118] 4-H-Benzyl-1,2,4-triazoles isomerize at 180°C to 1-benzyl-1,2,4-triazoles.[2.119]

x-(1H-Triazol-1-ylmethyl)phenols and -anilines are synthesized from 1-hydroxymethyl-1,2,4-triazoles.[2.120]

Triazolylmethyl-benzeneamines inhibit *Aspergillus flavus*, *A. parasiticus* and *Fusarium solani*,[2.121] but show low activity against *Candida albicans*, *Penicillium* spp. and *Microsporum gypseum* when compared to their imidazole analogs **2.18**. Degradation in soil of 1-benzyl-1,2,4-triazoles has been investigated for similar compounds with F, Cl, CF_3 , methoxy and butyl as aromatic substituents. Decomposition increases with moisture and temperature as expected, and is fastest without an aromatic substituent.[2.122]

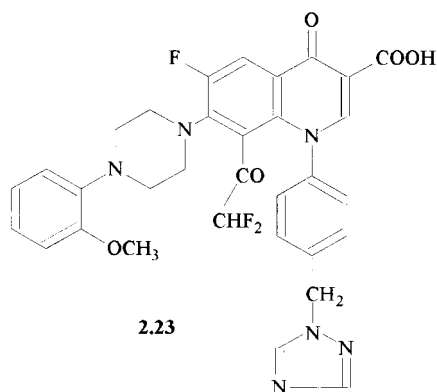
Compounds **2.21** show virucidal activity.[2.123]

From the series above, compound **2.22**, ZD-1033 or arimidex [120511-73-1] is being developed for the treatment of breast cancer for post-menopausal women who have relapsed after hormonal therapy.[2.124]



The ^{14}C -1,3,4-triazole-labeled form of ZD-1033 has been prepared.[2.125]

In other more elaborate derivatives of **2.14**, substituent X represents the 1-position of 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids to form compounds **2.23** with high activity against HIV in human lymphocytes.[2.126, 2.127, 2.128]

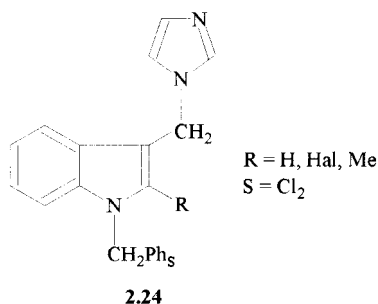


2.5 Heteroarylmethyl- and heteroaryl-methylen-azoles

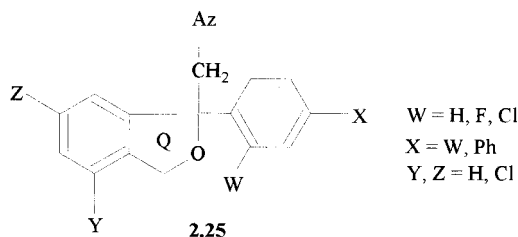
2.5.1 Imidazoles

1-Imidazol-1-yl-methyl-furans show only minor antifungal activity.[2.129]

3-(1H-Imidazolylmethyl)-indoles **2.24** inhibit *Cryptococcus neoformans* (the cause of fatal meningitis in humans) and *Candida pseudotropicalis*. [2.130, 2.131]



2-(1H-Imidazol-1-ylmethyl)-1,3-dihydroisobenzofurans inhibit *C. albicans*, *C. tropicalis* and *C. stellatoidea*, and vaginal yeast infection of hamsters.[2.132, 2.133, 2.135, 2.161] Optimal compounds **2.25** with Az = Im; W, Y, Z = H; X = Cl have been compared with rotamer forms of miconazole.[2.134]

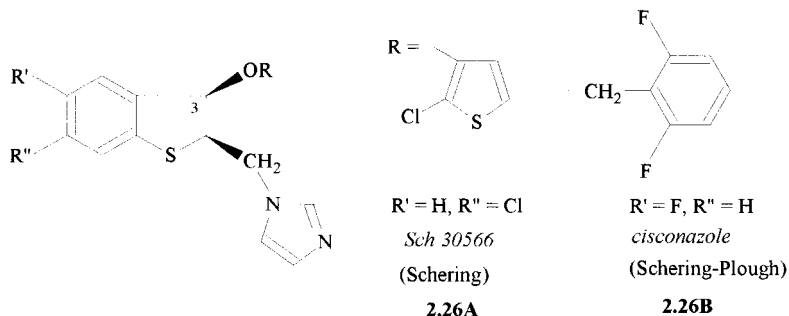


These substances also include one in which imidazole has been replaced by 1,2,4-triazole, or the fused dihydro-ring Q by pyran or thiopyran.[2.134] Some of these compounds prevent *Puccinia recondita* on wheat and also show plant growth inhibition.[2.161]

2-(1H-Imidazol-1-ylmethyl)-dihydrobenzothiophens **2.26A** and **2.26B** constitute a new class of azolyl fungicides, with main activity against *Cryptococcus neoformans*, and some also against *Candida pseudotropicalis* and *Geotrichum candidum*. [2.135, 2.136, 2.137, 2.138, 2.139, 2.140, 2.141]

(These series can also be regarded as cyclic analogs of 1-(3-hydroxyalkyl)1H-azoles, which are discussed in section 3.6.2).

Further development has resulted in Sch 30566, Sch 31153 and its fluoro analog **2.26B**, cisonazole [104456-79-3]. In a slow-release vaginal suppository, cisona-



azole is superior to a similar preparation of miconazole in hamsters suffering from vaginal *Candida albicans* infection.[2.142]

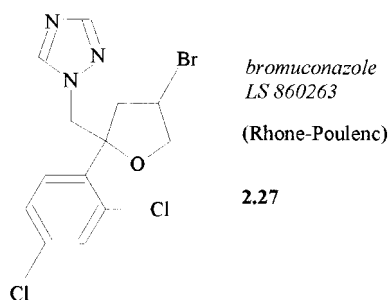
6-(1H-Imidazol-1-ylmethylene)-quinazolin-5-one shows remarkable activity against *Candida krusei*. [2.143]

3-(1H-Imidazol-1-ylmethyl)coumarins inhibit i.e. *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. [2.144]

2.5.2 Azoles

Azolythiazoles and azolylmethylthiazoles have been claimed as medical fungicides and bactericides.[2.145]

2-(1H-Azolylmethyl)-tetrahydrofurans and -thietans have been disclosed for their potential in the treatment of fungal infections of plants.[2.146, 2.147, 2.148, 2.149, 2.150, 2.151] From these, the tetrahydrofuran derivative **2.27**, bromuconazole [116255-48-2] has been developed which controls Ascomycetes, Basidiomycetes and Fungi imperfecti in a large number of crops.



Bromuconazole also controls plant diseases not normally sensitive to triazoles, such as *Fusarium roseum* and *Alternaria* spp.[2.152, 2.153, 2.154, 2.155, 2.156, 2.157]

(For x-(1H-Azol-1-ylmethyl)-y-hydroxymethyl-tetrahydrofuranes, -tetrahydropyranes and their derivatives see sections 6.1.10, 6.12 and 6.2.4.)

6-(1H-Azol-1-ylmethyl)-2-quinazolones have been claimed for their complete suppression of vaginal keratinization in ovariectomized rats.[2.158]

3-Azol-1-ylmethyl-thiochromanones, -benzochromanone, -benzothiochromanones and - α -tetralones have been prepared from the appropriate Mannich bases.[2.159]

Similar x-(1H-azol-1-ylmethyl)-benzocyclopentanes, -benzocyclohexanes, -benzopyrans and -benzothiopyrans constitute part of a larger claim for new antimycotics.[2.132, 2.160]

2-(1H-Azol-1-ylmethyl)-benzothiophenes, -benzofuranes, -chromans and -thiochromans show protozoacidal activity.[2.135]

Azol-1-ylmethyl-cyclopentabenzopyrans control *Puccinia recondita* spores.[2.164]

2.5.3 Triazoles

(For (1H-triazolylmethyl)-thiazolidines, isoxazolidines, isoxazolines, -oxazolines, 1,3-dioxolanes, 1,3-dioxacycloalkanes and tetrahydrofuranes see section 6.1.)

Pyrazole analogs of the title compounds are inactive as fungicides.[2.166]

(1H-Azol-1-ylmethyl)-tetrahydropyrans and related oxathiolanes have been claimed as antibacterials and antifungals.[2.167, 2.168]

2-(1,3,4-Oxadiazolin-5-yl)-5-phenyltetrazoles have been evaluated as antibacterials.[2.169]

2.6 1-(2-Phenyl- and 2- heterocyclyl)ethyl-azoles

2.6.1 Pyrazoles

2.6.2 Imidazoles

3-(or 5-)Methyl-1-(2-phenylethyl)pyrazoles have been prepared by three different methods.[2.174, 2.175]

'Plain' 1-[2-(chlorosubstituted phenyl)ethyl]azoles **2.27a** (R^1 , R^2 = H; X_2 = 2,4-Cl₂) are part of wider claims for fungicides associated with hypolipidemic effects.[2.170, 2.171, 2.172]

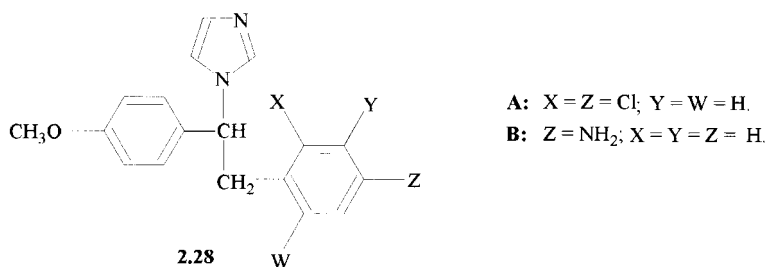
Im

$$(\text{CH}_2)_{n^1} \quad n, n^1 = 0, 1, 2$$
$$\text{R}^1\text{CR}^2 \quad \text{R}^1, \text{R}^2 = \text{H, alkyl}$$
 $(\text{CH}_2)_n\text{Ph}_x$

2.27a

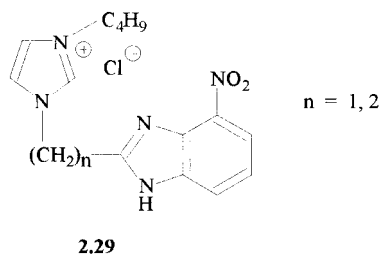
These substances control *Helminthosporium teres* on barley, *Erysiphe polygoni* on beans, and *Puccinia recondita* on wheat. (For a closely related antifungal structure, which has been developed into the hypolipidemic drug azalanstat, see section 6.2.1.) These and other related compounds have been part of a program for fertility regulation agents.[2.173]

1,2-Diaryl-1(1H-imidazol-1-yl)ethanes **2.28** are active against a number of *Candida* species.[2.176, 2.177]



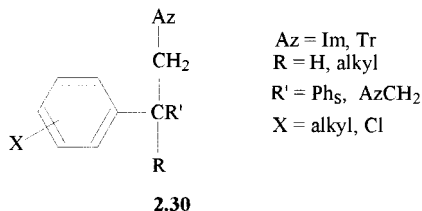
Best examples carry substituents Z = Cl or NH₂ or X, Y = 2,4-Cl₂.

Quaternary salts of 1-(2-heterocyclyl)ethyl-imidazoles **2.29** show *in vitro* and *in vivo* activity against *Trichomonas vaginalis*. [2.178]



2.6.3 Azoles

Phenylethyl-azoles **2.30** can be prepared from the appropriate halides and sodium azoles and show excellent control of *Erysiphe graminis*. [2.179, 2.180]



Derivatives with an additional phenyl in the α -position are prepared from 1-benzylazoles via α -lithiation.[2.180] For other 1-(2-phenethyl)-azoles see.[2.175]

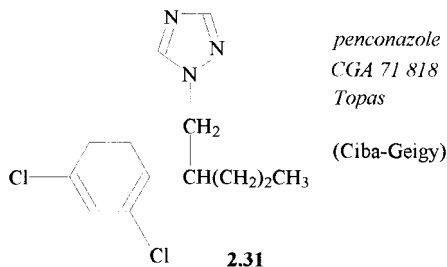
Homologous structures like 1-(1H-azol-1-ylmethyl)cyclopropanes inhibit *Puccinia recondita* on wheat seedlings and *Podosphaera leucotricha* on rice and soy beans.[2.181, 2.182]

1-(1H-Azol-1-yl)methylcyclobutanes have similar activities.[2.183, 2.184]

2.6.4 Triazoles

1-(2-Phenylethyl)-1,2,4-triazoles can be prepared from the appropriate halides or mesylates and sodium triazole in DMF,[2.185] or by constructing the triazole ring as the last synthetic step from a hydrazine derivative Ph₅CHPrCH₂NHNHCOCH₃ by cyclocondensation with formamide.[2.186] Another route starts from a 1-(chloromethyl)-1-H-azole and (EtO)₂PONa followed by a Wittig reaction.[2.187]

A number of these compounds have been tested by Hansch analysis concerning their activities against *Erysiphe graminis*,[2.188] against *Drechslera sorokiniana*, *Piricularia oryzae*, and in the yeast demethylase assay.[2.189] Among a series of analogs of myclobutanil (see section 4.11), several active 1-[1H-(2-phenyl)hexyl]-azoles have been subjects of a Hansch analysis.[2.189, 2.190] From these compounds the top-fruit fungicide penconazole **2.31** [66246-88-6] has been developed.[2.191, 2.192, 2.193]



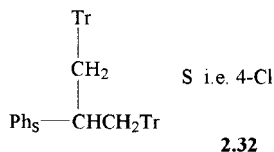
Penconazole controls *Podosphaera leucotricha* infections of apples, *Uncinula necator* and *Guignardia bidwellii* on grapes, and *Venturia* on pome fruits.[2.193] It is rapidly decomposed by UV radiation to a triazolo-[5,1-a]-isoquinoline.[2.194] Several compositions have been claimed.[2.195]

Penconazole exhibits the highest vapor pressure at 25°C of nine azole fungicides.[2.196] For veterinary applications, the agent is therefore easily evaporized.[2.197] A water-based emulsion has also been developed.[2.198]

1-(3-Phenylalkyl)azoles[2.199], 1-(2,x-diarylalkyl)azoles [2.200] and their heterocyclic analogs,[2.201, 2.202] have all been claimed as fungicides.

1,3-Bis(1,2,4-triazol-1-yl)propane derivatives such as **2.32** are claimed for their strong antimycotic action against *Candida* kidney infection of mice.[2.203, 2.204]

A parenteral formulation has been developed.[2.205]

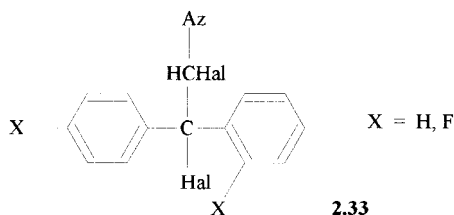


2.7 1-(x-Halogeno and x,y-dihalogenoalkyl)1H-azoles

2.7.1 1-Halogeno- and 1,2-dihalogen-1-azolylalkanes

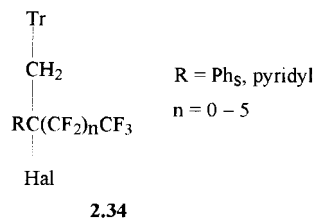
2-Halogenoalkyl-1-azolylalkanes can be prepared from the azole, an aldehyde and sulfonyl chloride, and have been claimed as fungicides.[2.206, 2.207, 2.208] 1-Fluoro-1-azolyl-2,2-diarylethanes show inhibition of *Staphylococcus aureus* and *Candida albicans*. [2.209]

1,2-Dihalogeno-1-azolylethanes **2.33** are similarly prepared from 1-halogenoaldehydes and SOCl_2 or from 1-(1H-azolyl)ethenes and chlorine or bromine.[2.210, 2.211] They control *Pyrenophora teres* and *Erysiphe graminis* on barley.



2.7.2 2-Halogeno-1-azolylalkanes

2-Halogenoethyl-1-pyrazoles, -triazoles or -tetrazoles can be prepared from the azoles and 1,2-dichloroethenes by PTC,[2.212] or from the corresponding 2-hydroxyethyl-1-azoles with bromine- PCl_3 , [2.213] A number of 1-alkyl-(2-halogenoalkyl)-1-azoles,[2.214] 2-halogeno-2-aryl-2-perfluoroalkyl-1-azoles **2.34**, [2.215, 2.216] and 2-halogeno-2,2-diaryl-ethyl-1-azoles, have all been claimed for their *in vivo* activity (mice) as medical fungicides, and for the control of *Sphaerotheca fugilinea* on cucumber.[2.217, 2.218]



Compounds related to **2.34** incorporate a second azole ring in place of the perfluoroalkyl group and inhibit *Candida albicans* infection in mice.[2.219, 2.220, 2.221, 2.222, 2.223]

2.7.3 3-Halogeno-1-azolylalkanes

1-[1-(2,4-Dichlorophenyl)-2,2-dichlorocyclopropylmethyl]-azoles inhibit *Erysiphe graminis* on barley.[2.224]

2.8 1-(x-Arylalkyl)-1H-azoles

(See sections 2.4.2 and 2.6.4).

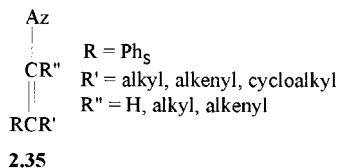
2.9 1-(Alkenyl and alkynyl)-1H-azoles and their halogen derivatives

2.9.1 1-(1-Alkenyl)azoles

2.9.1.1 1-(1-Alkenyl)imidazoles

Title compounds **2.35** can be prepared

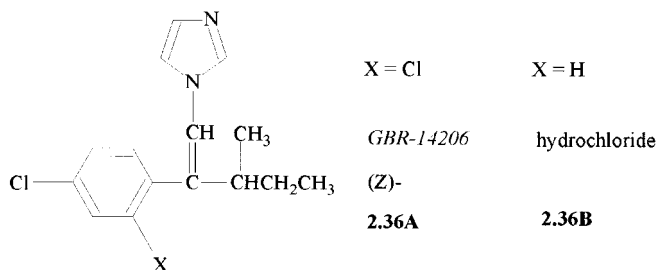
- by dehydration of 1-(2-hydroxyalkyl)azoles,[2.225, 2.226, 2.227, 2.228, 2.229]
- by vinylation with alkynes,[2.230, 2.231]
- by reaction of ketones with 1-[bis(trimethylsilyl)methyl-1,2,4-triazole, with N',N'-sulfinylimidazole,[2.232, 2.233] or with diethyl (1H-1,2,4-triazol-1-yl)methyl phosphonate,[2.234]
- by dehydrohalogenation of 1,1-dihalogenalkanes followed by condensation with an azole,[2.235] or
- by chlorination/dehydrochlorination of carbinols. [2.236]



1-Halovinyl-1-azoles are formed from 1,2-dihalogenalkylazoles by partial dehydrohalogenation.[2.237]

Fitting structure **2.35** with $\text{R}', \text{R}'' = \text{H}$ and $\text{R} = \text{C}_6\text{H}_4\text{Cl}$ or $\text{C}_6\text{H}_3-2,4\text{Cl}_2$ produces compounds with moderate antifungal activity.[2.233] However from similar series, compounds with $\text{R} = \text{Me}_3\text{C}-$, $\text{R}' = 2,4-\text{Cl}_2\text{C}_6\text{H}_3\text{CH}_2-$, and $\text{R}'' = \text{H}$ show strong inhibition of *Staphylococcus aureus* and *Trichophyton mentagrophytes*.[2.236] One other example of compounds **2.35** with $\text{Az} = \text{Tr}$, $\text{R} = 2-(4\text{-chlorophenylethyl})-$, $\text{R}' = \text{tert. butyl}$ and $\text{R}'' = \text{H}$ strongly inhibits *Fusarium oxysporum*, *Phytophthora infestans*, and *Sclerotium rolfsii*.[2.234]

In general, Z-isomers are more potent against *Candida* and E-isomers more active against *Trichophyton rubrum*, but agent GBR-14206, **2.36A** [123414-70-0] stands out with optimum activities against both species.[2.238]



An injectable emulsion of **2.36B** has been successful in the treatment of mice infected with *Candida albicans*.[2.239] The hydrochloride of its monochloroderivate [88607-90-3] inhibits *Drechslera sorokiniana* on barley seeds.[2.240]

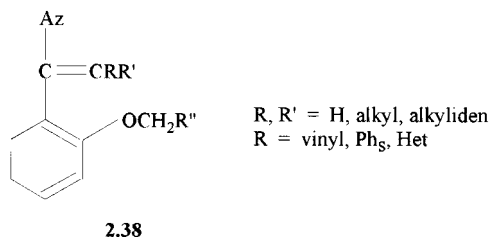
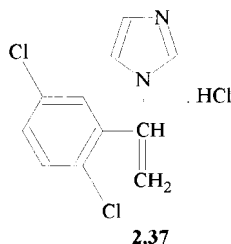
Still another example of the general structure **2.35** with $\text{R}' = \text{H}$, $\text{R} = \text{R}'' = 2\text{-ClC}_6\text{H}_4-$ protects bean plants against *Erysiphe polygoni*.[2.241]

2.9.1.2 1-(1-Alkenyl)-1H-triazoles

Still covered by the general structure **2.35**, a group of compounds with $\text{Az} = \text{Tr}$, $\text{R} = \text{R}' = 4\text{-ClC}_6\text{H}_4-$ and $\text{R}'' = \text{H}$ has been suggested as agricultural fungicides which control *Pyricularia oryzae* on rice plants.[2.235] Other series, characterized by $\text{R} = 2,4\text{-Cl}_2\text{C}_6\text{H}_3-$, $\text{R}' = \text{C}_3\text{H}_7\text{-n}$, $\text{R}'' = \text{H}$ and by $\text{R}'' = \text{Cl}$, $\text{R} = 4\text{-FC}_6\text{H}_4-$ and $\text{R}' = 2\text{-F-}$ or $2\text{-ClC}_6\text{H}_4-$ inhibit *Puccinia* species on wheat.[2.225, 2.228, 2.237]

2.9.2 1-Styrylazoles

Compound **2.37**, active against *Trichophyton rubrum*, represents an oxygen-free example of the title compounds of the general formula **2.38**. [2.242]

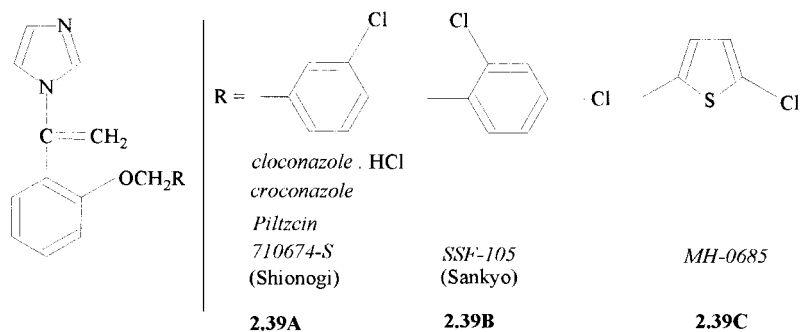


In a number of applications, compounds **2.38** have been claimed as medicinal, agricultural and industrial bactericides and fungicides due to their activity against *Penicillium citrinum*, *Cryptococcus neoformans*, and *Trichophyton rubrum*. [2.243, 2.244, 2.245, 2.246, 2.247, 2.248, 2.249, 2.250, 2.261, 2.262, 2.263, 2.264, 2.265] Some have been suggested as industrial and domestic fungicides and bactericides, using their toxicity to *Cladosporium herbarum* and *Chaetomium globosum*. [2.251]

The medicinal chemistry of compounds **2.38** is covered by a full paper. [2.267] Optimal substituents against *Trichophyton mentagrophytes*, *T. rubrum* and *Candida albicans* are R, R' = H, Me; R'' = C₆H₅CH₂, 4-ClC₆H₄CH₂, 3-ClC₆H₄CH₂, 3,4-Cl₂C₆H₃CH₂, and 2-Chlorthienyl-3-methyl-; and R''' = H, 5-Cl, and 3,5-Cl₂. Replacing imidazole by 1,2,4-triazole lowers antimicrobial activity. The same group of compounds has been investigated by computer automated structure correlations (CASE) and QSA methods. Good correlations have been achieved for activities against *Candida albicans* and *Aspergillus fumigatus*, [2.268] and against *Botrytis cinerea*, [2.269] with hydrophobicity as the most important positive parameter. Under greenhouse conditions, there is a negative effect caused by the mobility of the agents on the leaf. [2.270]

Further variations of the general structure **2.38** by exchange of AzCH₂ for Az, have resulted in fungicides which can be used to treat cucumbers against *Sphaerotheca fuliginea*. [2.271] Replacing the benzene substructure with naphthalene resulted in activity against *Bacillus subtilis*. [2.272]

From these, cloconazole **2.39A** [base, 77175-51-0; hydrochloride 77174-66-4], agent **2.39B**, SSF-105 and compound **2.39C**, MH-0685 [105688-63-9] have been developed as antifungal agents.[2.106, 2.252, 2.253, 2.254, 2.255]



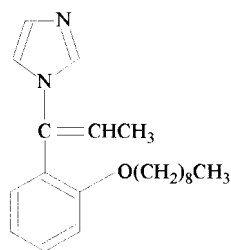
Stable complexes of an isomer of **2.39A** with $R = C_6H_4-4Cl$, i.e., with phenolphthalein, are useful against *Botrytis cinerea*. [2.256] Pharmaceutical preparations have been developed for croconazole, [2.257, 2.258, 2.259] and phenolic metabolites have been proposed. [2.260]. Croconazole also exerts an antiphlogistic effect in experimental animals. [2.253]

Compound **2.39B** promises to be a potential agricultural fungicide with *in vivo* activities against *Botrytis cinerea*, *Sclerotinia sclerotiorum* and *Sphaerotheca fuliginea*. [2.255]

Agent **2.39C** exhibits potent activity against *Trichophyton*, *Epidermophyton*, and *Microsporum* spp. [2.250]

A substance 711389-S, related to series **2.39**, in which R is replaced by $-CH(OH)CH_2NHCH(CH_3)_2$ has been investigated as antiarrhythmic agent. [2.255]

One compound **2.40** can be used for the protection of paint against fungi such as *A. niger* and *P. citrinum*, [2.264] another inhibits *Chytridiomyces*. [2.265]

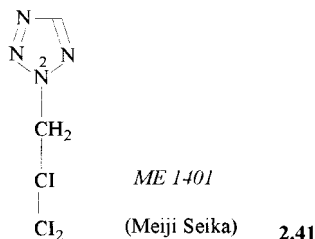
**2.40**

2.9.3 1-(Allyl- and 1-propargyl)-1-azoles and their homologs

2.9.3.1 1-Allyl 1H-azoles

Pyrrole on N-allylation with vinyltriphenyl phosphonium bromide, an aldehyde and NaH in THF yields mainly (*Z*)-products, while (*E*)-products predominate with the vinyl tributylphosphonium reagent.[2.273] Pyrrole is triiodoallylated with 3-diiodo-2-iodoallyl tosylate to form 1-(3-diiodo-2-iodoallyl)pyrrole which inhibits infection of guinea pigs with *Trichophyton mentagrophytes*. [2.274] In the same series, 2,3-dichloro-, or 2- or 3-nitrosubstituted pyrroles have resulted in products which high antifungal activity but also with inherent synthetic problems.[2.275]

Azoles can be 1-allylated without solvent under PTC.[2.276] 1,2,4-Triazole and tetrazoles on 1-triiodoallylation produce compounds which inhibit *Candida albicans* and *Aspergillus flavus*. [2.277, 2.278] The tetrazole derivative ME 1401, **2.41** seems to be particularly useful with an antimicrobial potency similar to clotrimazole; no cross-resistance to any other antifungal agent has been seen.[2.279]

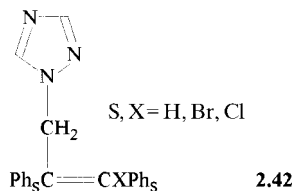


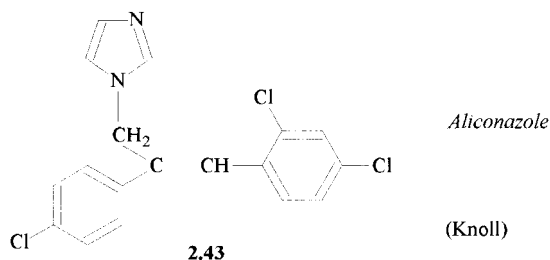
However, the development of ME 1401 has been discontinued.[2.280] Triiodoallyl-pyrrole TA-2 and -imidazole TA-10 and their tetrazole analogs inhibit industrially harmful fungi.[2.281]

Further bactericidal and fungicidal derivatives of **2.41** are substituted with alkyl, Ph_s or benzyl at position 5 of the tetrazole.[2.275, 2.277, 2.282] Quantitative structure—activity relationships (QSAR) show that anti-*Candida* activity of the triiodoallyl-azoles discussed above is positive linear, while that of anti-*Trichophyton mentagrophytes* activity runs parabolic to hydrophobicity. Steric requirements result in lower potency.[2.275]

General structures **2.42** have been claimed as agricultural fungicides which inhibit *Puccinia recondita* and *Erysiphe graminis* on wheat, and *Pyrenophora teres* and *E. graminis hordei* on barley.[2.283, 2.284, 2.285, 2.286, 2.287]

From these, aliconazole **2.43** [63824-12-4] has been developed as topical anti-mycotic.[2.288]





A group of 1-[2-(2-substituted hydroxy- 5-substituted phenyl)allyl]-imidazoles with activity against *Botrytis cinerea* has been evaluated by QSAR; again, hydrophobicity is the most important positive parameter.[2.270, 2.289]

1-(2,3-Diarylallyl)imidazoles and their heterocyclic analogs have been claimed as fungicides.[2.200, 2.201, 2.290, 2.291] The same activity has been found in 1-(1-azolyl)-5-phenyl-4-penten-3-ones.[2.290]

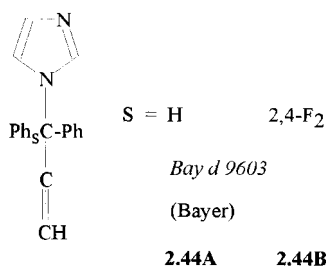
In fungicidal 1-(α -imidazol-1-yl)cyclohexenes the double bond of the allyl group is part of a carbocyclic ring.[2.292]

2.9.3.2 1-Propynyl-1H-azoles

Title compounds can be prepared with high regioselectivity from imidazole, propargyl bromide under microwave activation and MgO catalysis,[2.293] or by PTC,[2.294] or from imidazole, acetylene and $(\text{PhO})_2\text{P}(\text{O})\text{H}$.[2.294] Azoles such as pyrrole and tetrazole can be iodopropargylated by iodopropargyl tosylate; the products inhibit *C. albicans* and *Aspergillus flavus*.[2.274, 2.277, 2.278]

Compound **2.44A**, Bay d 9603 [36698-20-1] shows broad-spectrum antifungal activity, a high rate of absorption and a relatively long half-life; on oral dosage it accumulates in the skin of experimental animals.[2.295] The agent also controls *Pseudocercospora herpotrichoides* on winter wheat.[2.295, 2.296]

2,4-Difluorophenyl-phenyl-propynes **2.44B** show excellent activity against *Leptosphaeria nodorum* on wheat.[2.297]



Iodopropargyl-imidazoles and -tetrazoles inhibit particularly fungi harmful for industrial products.[2.281]

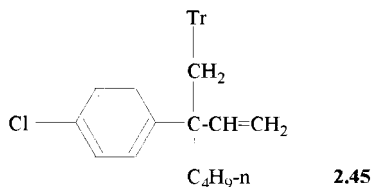
Optimal N-iodopropargyl compounds have been derived from 5-lower alkyl- or 5-phenyltetrazole.[2.275, 2.298] QSAR analysis demonstrates the importance of hydrophobicity, electronegativity and steric effect similar results for iodopropar-

gyl-azoles, but somewhat lower anti-*Candida* potencies as compared with the triodoallyl-azoles discussed above.[2.275]

1-(4-Butynyl-azoles inhibit *E. graminis* on barley. They can be purified by crystallization of the 1,5-naphthalenedisulfonates.[2.299]

2.9.3.3 1-(But-3-en-1-yl)azoles

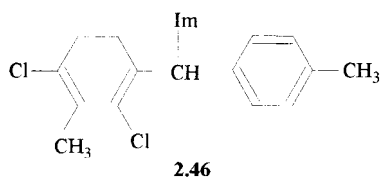
Compound **2.45** illustrates part of a larger claim for agrochemical fungicides which control e.g. *Erysiphe graminis*.[2.300]



2.10 1-Diphenylmethyl-1H-imidazoles

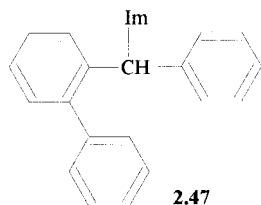
2.10.1 1-[1-Phenyl-1-(4-substituted phenyl)methylimidazoles

Title compounds form part of a large claim for agricultural microbicides.[2.301] For example, substance **2.46** inhibits *Phaseolus vulgaris* on kidney beans, *Pythium aphanidermatum*, *Fusarium oxysporum* and *Rhizoctonia solani*.

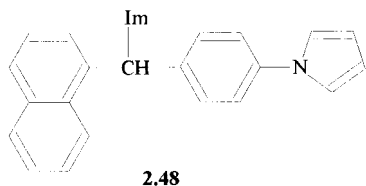


2.10.2 Biphenyl-phenylmethyl-1H-imidazoles

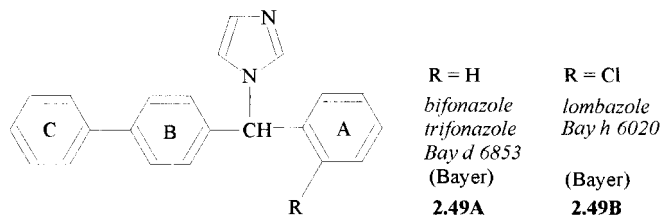
o-Biphenyl-1-ylphenylmethane **2.47** has been claimed as a medical fungicide.[2.302]



Compound **2.48** which is not only related to bifonazole, but also to naftifine, shows high activity against *Candida* strains.[2.303]



The most successful drug in this series however is bifonazole **2.49A** [60628-96-8].[2.304, 2.305, 2.306]



The success of bifonazole prompted a series of claims and papers for better synthesis.[2.112, 2.307, 2.308, 2.309, 2.310, 2.311, 2.312, 2.313, 2.314]

A series of 56 azole antifungal agents related to bifonazole, as discussed in sections 2.10 and 2.11, has been investigated by comparative molecular field analysis (CoMFA) to yield two models of alignment with predictive value.[2.315]

Bifonazole shows high *in vivo* efficacy against a number of dermatophytoses and candidoses, and also against Gram-negative microorganisms such as *Legionella*. [2.316] In comparison with several other standard antimycotics, bifonazole has been demonstrated to be a very weak allergen in humans.[2.317]

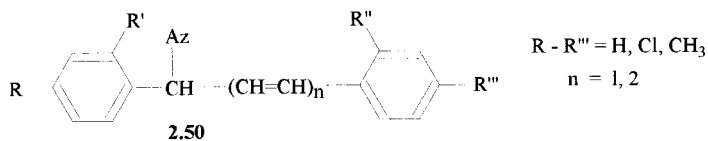
Lombazole **2.49B** [60628-98-0] displays maximum activity against *Corynebacterium* species, *Staphylococcus albus* and *Pityrosporum* species, and forms the active agent in the preparation Twent™ against acne vulgaris and acne juvenilis.[2.318]

For the indications given above, formulation is very important for bifonazole and lombazole.[2.319, 2.320, 2.321, 2.322, 2.323, 2.324, 2.325, 2.326, 2.327, 2.328, 2.329, 2.330] Bifonazole is characterized by a rather low solubility in water compared to other standard azole antimycotics. On complexing with β -cyclodextrin, solubility increases about 160-fold. Though the resultant complex appears to have lost activity against the common test organisms, addition of β -cyclodextrin to the aqueous phase of a galenic preparation (especially one with carbapol 1%), increases the inhibition zone size 2-to3-fold for *Candida albicans*, *A. niger*, *S. cerevisiae* and *T. cutaneum*. It seems that addition of the dextrin may result in a better release of the drug from its preparations. [2.331]

In experimental *Trichophyton mentagrophytes* or *Microsporum canis* infections of guinea pigs, oral bifonazole acts in the stratum corneum and in hair sheaths resulting in complete clearance within seven days.[2.332]

2.10.3 Vinylogs of 1-diphenylmethyl-1H-azoles

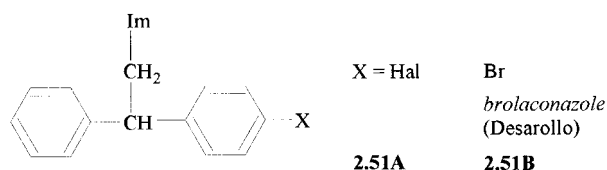
Some vinylogs **2.50** of bifonazole have been described.[2.333]



The best example (Az = Im, n = 1, R, R', R'' = Cl; R = Cl, R''' = CH₃) displays activity against *Candida albicans* and *C. paratropicalis*. [2.333] Others inhibit *Trichophyton mentagrophytes*, *Microsporum canis*, and *Aspergillus fumigatus*.

2.10.4 1-(2,2-Diphenylethyl)-1-H-azoles

1-(2-Diphenylethyl)azoles **2.51A** have been claimed as antimycotics and fungicides.[2.334]



They inhibit *C. albicans*, and control phytopathogens such as *Phytophthora infestans*, *Plasmopara viticola*, *Poria monticola*, *Ulocladium consortiale*, *Aureobasidium pullulans*, *Aspergillus niger* and *Bacterium subtilis*. [2.335] From these, the fungicide brolaconazole **2.51B**, [118528-04-4] and its nitrate, sulfate and tosylate salts have been studied in detail.[2.336]

Interesting activity against *Piricularia oryzae* on crops, fruit, vegetable and ornamental plants has been observed, and use for the protection of wood and varnishes has been proposed.

2.11 Heterocyclic analogs of 1-(diphenyl)methyl-1H-azoles

2.11.1 1-(Heterocycl-phenyl)methyl-1H-azoles

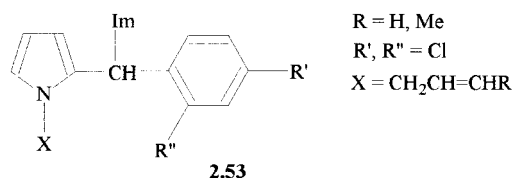
Replacing one or two phenyls of bifonazole **2.49A** by heterocyclic rings to arrive at structures **2.52** has been a favored strategy in the work originating from the university La Sapienza Rome, Italy.

Az

Ar¹CHAR²

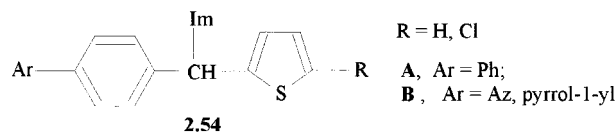
2.52

Such antifungal compounds, with Ar¹ = pyrrol-3-yl, **2.53** have been found to be as potent as ketoconazole, and half as potent as bifonazole against *Candida albicans*. [2.337]



Introduction of *trans*-CH=CH-COOEt or n-propyl at the 1-position of pyrrol does not influence the level of activity. [2.338] Antimicrobial potency is however strongly reduced by replacing X with methyl or cyclopropylmethyl. [2.339]

With Ar² = thienyl, derivatives **2.54A** and **5.54B** have been claimed as useful antimycotics with demonstrated *in vitro* inhibition of *Candida albicans* comparable to the standards. [2.341]

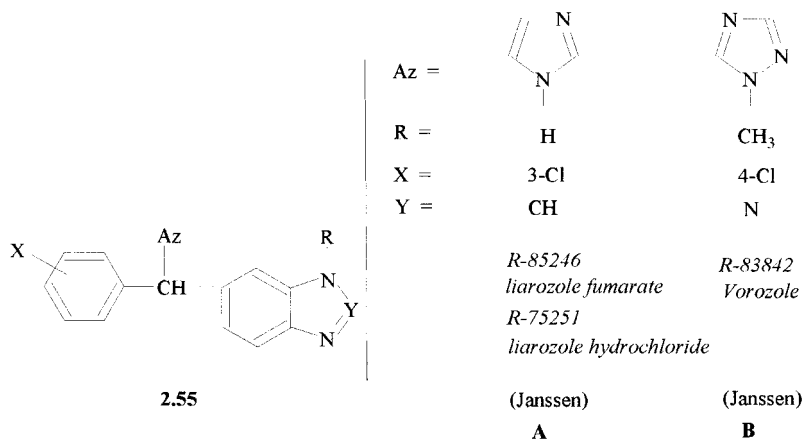


With Ar² = pyrazol-1-yl, compound 1,1'-Bis-pyrazolyl-(thiophen-2-yl)methane shows little antimycotic activity compared to clotrimazole. [2.340]

Replacing Ar in **2.54** by pyrazole, imidazole or 1,2,4-triazole sharply reduces activity against fungi in that order, and nitrogen aliphatic rings such as piperidin or piperazin eliminate it altogether. [2.340]

Modifying structure **2.52** with Ar² = benzimidazol-5-yl or benzotriazol-6-yl has resulted in potential anticancer agents liarozole and vorozole. [2.342]

Liarozole fumarate **2.55A**, [(±) 145858-52-2] is expected to be efficacious in the treatment of prostate cancer.[2.343]

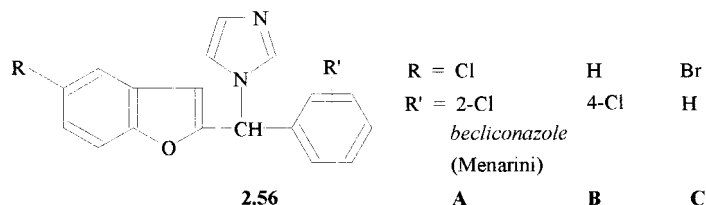


Separate (-)- and (+)-enantiomers have been claimed.[2.344, 2.345] Liarozole is devoid of antifungal activity and does not affect the biochemistry of cholesterol in humans.[2.346]

Vorozole **2.55B**, [129731-10-8] is hoped to present a new tool in the control of estrogen-dependent breast cancer. Its main activity rests in the (+)-enantiomer.[2.347]

Title compounds **2.52** with Ar² = 1,4-benzoxazin-6-yl show bactericidal activity.[2.348]

Title compounds **2.562** with Ar² = benzofuran-2-yl, **2.56** have been reported as bactericides and antimycotics.[2.132, 2.349, 2.350]



From these series, optimal compounds becliconazole **2.56A**, [112893-26-3] and agent **2.56B** [111790-32-0] display pronounced *in vitro* antifungal activity against *Candida*, *Trichophyton*, and *Microsporum* genera and against non-dermatophytes like *Aspergillus* and *Penicillium* spp.; their toxicity to *Torulopsis glabrata*, *Rhodotorula* spp. and *Cryptococcus neoformans* surpasses that of the standards.[2.351, 2.352]

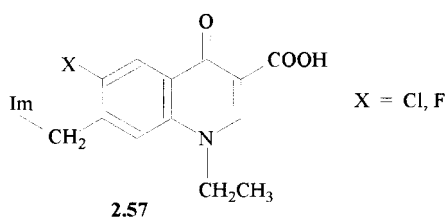
As demonstrated by GMS-MS, both **2.56A** and **2.56B** achieve higher concentrations (by factors of 3.6 and 2.6 respectively) in rabbit plasma 2 hours after topical application than bifonazole.[2.353] 5-Deschloro becliconazole has been sepa-

rated into the enantiomers which are much more stable against racemization at pH 7.4 than (+)-econazole.[2.354]

The bromo derivative **2.56C** shows excellent inhibition of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. [2.349]

Title compounds with $\text{Ar}^2 = \text{benzothiophen-3-yl}$ and an optimal 3-chlorophenyl for Ar^1 demonstrate good *in vitro* activity against pathogenic yeasts and dermatophytic fungi.[2.355]

Title compounds **2.572** with $\text{Ar}^2 = 1,4\text{-dihydroquinoline-6-yl-3-carboxylic acid}$, a partial structure of norfloxacin, **2.57** inhibit *Bacillus subtilis* and *Escherichia coli*. [2.356]

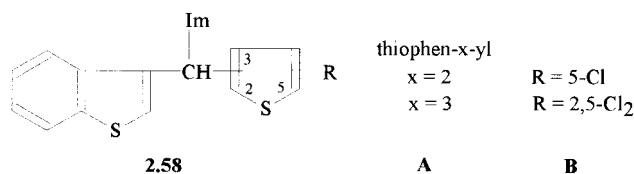


(Compare also section 2.5.1 and compound **2.23**).

Finally, compounds **2.52** with $\text{Ar}^2 = \text{isoquinol-1-yl}$ have resulted in an optimal example with a 4-benzylphenyl for Ar^1 , displaying half the activity of the standards against *Candida albicans* strains.[2.357]

2.11.2 1-Di(heterocyclyl)methyl-1H-azoles

One paper includes 1-[di(heterocyclyl)methyl]-1H-imidazoles. Optimum examples **2.58A** and **2.58B** with benzo[b]thiophen-2-yl and 5- or 2,5-dichlorothiophen-3-yl as Ar^1 and Ar^2 , display *in vitro* activity against pathogenic yeasts and dermatophytes only slightly inferior to bifonazole.[2.355]

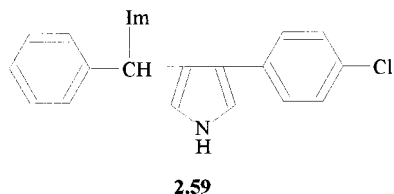


2.11.3 Heterocyclic analogs of 1-(biphenyl-phenyl)methyl-1H-azoles

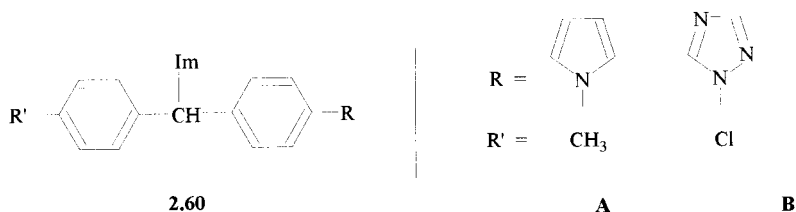
Each of the three phenyl groups A, B and C in bifonazole **2.49A** has been replaced by heterocycles.

Replacement of phenyl A by 5-phenylthien-2-yl results in compounds **2.54A** (see section 2.11.1). Ring A can also be replaced by 4-biphenyl-4-yl or 1-naphthyl without losing activity.[2.303, 2.361]

Replacing phenyl B by pyrrol-3-yl, with phenyl C in pyrrol positions 1, 3 or 4, has arrived at optimal compounds with *in vitro* activities against *Candida albicans* and *Candida* spp. comparable with those of the standards.[2.358, 2.359, 2.360] From these, **2.59** displays better topical efficacy in experimental cutaneous candidiasis of rabbits than bifonazole. [2.359]



Replacement of ring C of bifonazole by pyrrol-1-yl,[2.362, 2.363, 2.364] by 1H-imidazol-1-yl or 1,2,4-triazol-1-yl,[2.365] has yielded optimal compounds **2.60A** and **2.60B**.



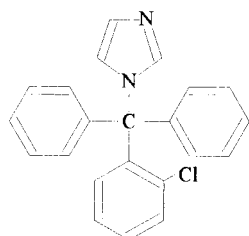
2.11.4 Di-heterocyclic analogs of 1-(biphenyl-phenyl)methyl-1H-azoles

Simultaneous replacement of two phenyls of bifonazole by heterocyclics concerns phenyl rings A + C [2.340] and B + C,[2.338] has produced the optimal substance **2.54B**.

2.12 1-Trityl-1H-imidazoles

2.12.1 Clotrimazole: Chemical and pharmaceutical aspects

Clotrimazole **2.61** [23593-75-1], one of the first azolyl antimycotic drugs, is still much prescribed and one of the standards against which new developments are compared.[2.366]



clotrimazole
Canesten
Bay b 5097
 (Bayer)

2.61

It combines good skin penetration with broad-spectrum activity against dermatophytes, yeasts,[2.367] *Aspergillus*, *Malassezia furfur*, and inhibits *Corynebacterium minutissimum*, *Staphylococci*, *Streptococci* which all may accompany mycotic infections. In the treatment of tinea infections and cutaneous candidiasis of skin and mucous membranes such as vaginal candidiasis, clotrimazole can be used as a single dose.[2.366]

An account of the investigators has summarized the ideas and hypotheses along which optimization of structure was achieved.[2.318] Curing rates of *Candida* infection of the mouse after systemic application are connected with

1. the hydrolysis rates of the C-N bond (carbocation formation),
2. the lipophilicity of the molecule (transport phenomena), and
3. its steric structure (fitting at the site of action); favorable influence of ortho-substitution (exaggeration of the trityl-propeller).

However, no clear-cut relationships could be worked out with the QSAR methods of Hansch and of Free-Wilson, since some of the mathematical properties of the biological results lacked sufficient precision. Rank correlations are useful and confirmed the superiority of ortho-substitution for antimycotic activity. A more recent investigation demonstrated the relation of lipophilicity with maximum surface area (as expressed by chromatographic parameters).[2.368]

The importance of clotrimazole has challenged a world-wide search for improved and alternative synthetic methods [2.112, 2.369, 2.370, 2.371, 2.372, 2.373, 2.374, 2.375, 2.376, 2.377, 2.378, 2.379, 2.380, 2.381, 2.382, 2.383, 2.384, 2.385, 2.386, 2.387, 2.388, 2.389, 2.390, 2.391, 2.392, 2.393, 2.394, 2.395, 2.396] which have been reviewed recently.[2.397]

The low solubility of clotrimazole (5.5 $\mu\text{mol/L}$)[2.331] has presented a challenge to find suitable galenic preparations for topical,[2.330, 2.398, 2.399, 2.400, 2.401, 2.402, 2.403, 2.404, 2.406, 2.407, 2.408] and vaginal applications,[2.324, 2.326, 2.409, 2.410, 2.411, 2.412], for aerosols in pulmonary treatment,[2.413] for the treatment of herpes labialis,[2.414] and in ophthalmology using its efficacy against *Anthamoeba* spp.[2.415]

New applications as antimycotic have been suggested by incorporation in shoe insoles or sandals,[2.416] for cellulose or synthetic fibers,[2.417, 2.418] and for finishing underwear and socks.[2.419]

2.12.2 Clotrimazole: microbiological activity

Clotrimazole displays activity against Gram-negative microorganisms such as *Legionella*. [2.316] The detection of trypanocidal activity in the complex $\text{RuCl}_2(\text{clotrimazole})_2$ has given hope for a new remedy for Chagas disease, endemic in South America. [2.420] This observation stresses the importance of the stability constants of complexes of clotrimazole and other standard antimycotics with heavy metals. [2.421]

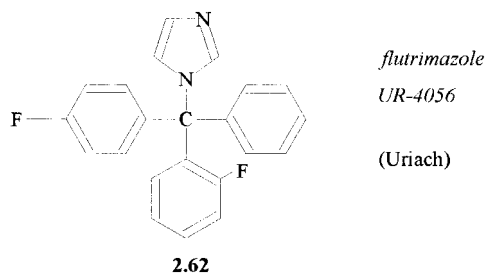
Clotrimazole, a potent inhibitor of epidermal metabolism of benzo[a]pyrene offers the chance to lower cancer risk caused by polycyclic aromatics in skin. [2.422, 2.423] It inhibits normal and cancer cell proliferation. [2.424] The drug has been recommended as a virucide in the treatment of *Herpes simplex*. [2.399] and shows promise in the treatment of sickle cell anemia. [2.425, 2.426, 2.427, 2.428] For this potential application, a HPLC assay has been developed to study pharmacokinetics after oral dose. [2.429] In this treatment, the effective agent seems to be the metabolite 2-chlorophenyl-bisphenylmethanol. [2.430]

Clotrimazole may serve as a novel antidiarrheal agent owing to its interference of K^+ transport. [2.433]

The emergence of strains resistant to clotrimazole, certainly an undesirable development in harmful microorganisms, has been turned into an advantage. Such chemical mutagenesis of brewing yeast gives a clotrimazole-resistant variety which shows an advantage in industrial alcoholic fermentation. [2.431, 2.432]

2.12.3 Flutrimazole

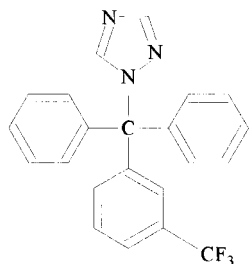
It is surprising that after 20 years of thorough investigation of clotrimazole and its related halogenated tritylimidazoles, the structurally similar flutrimazole **2.62** [119006-77-8] with improved properties could be introduced. [2.434, 2.435, 2.436]



Here, the hope has been realized that with the appearance of fluorinated instead of chlorinated metabolites, embryotoxicity can be lowered further in comparison to clotrimazole and less irritation might be seen. *In vitro* activity of flutrimazole seems to be equal or better than the standards, bioavailability is four-fold higher in dogs. [2.437] Flutrimazole was launched in 1995 as a topical antimycotic. [2.438] The drug also displays anti-inflammatory action. [2.439]

2.12.4 Further close analogs of clotrimazole

Flutrimazole must not be confused with *fluotrimazole* **2.63** [31251-03-3].[2.440]



2.63

fluotrimazole

Persulon

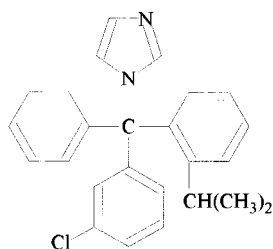
Bay Bue 0620

Bayer 6660

(Bayer)

Yet *fluotrimazole* with its somewhat limited fungicidal spectrum has been replaced by triadimefon (see section 4.7) with its much broader spectrum of antimicrobial activity.[2.440, 2.441, 2.442].

Another related compound, Bay d 6853, **2.64** [66642-47-5], shows a broad spectrum of antimicrobial activity, but suffers from insufficient absorption.[2.295]



2.64

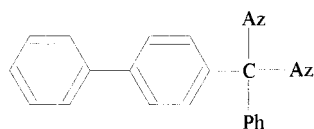
Bay d 6853

(Bayer)

2.13 1-Trityl-1-H-azoles with heterocycles replacing phenyl

General structures **2.65** have been claimed for their activity against *Epidermophyton floccosum*, *Trichophyton mentagrophytes* and *Microsporum gypseum*.[2.443]

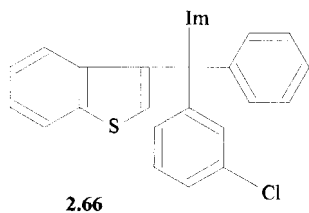
Some of these, after oral doses, decrease testosterone levels in rats.[2.444]



2.65

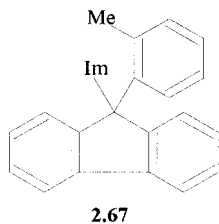
Az = Im, Tr, pyrazol-1-yl

Benzothiophen-yl replaces phenyl in a number of clotrimazole analogs, resulting in an optimal substance **2.66**.^[2.355]

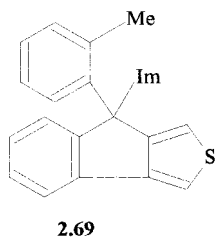
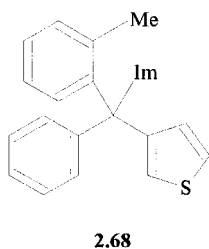


2.14 Tricyclic analogs of 1-diphenylmethyl-1H-azoles

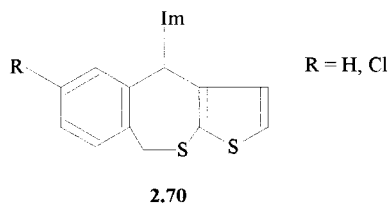
A dibenzocyclopentadiene derivative **2.67** has been recommended as part of an aqueous antimicrobial preparation for washing and finishing of textiles.^[2.445]



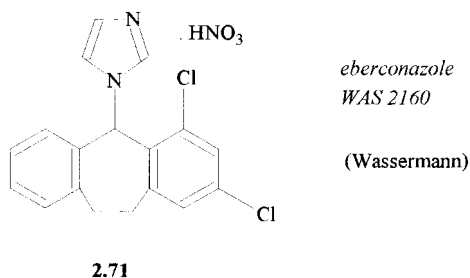
Similar indenothiophen derivatives **2.68** and **2.69** show antifungal efficacy in infected guinea pigs.^[2.446, 2.447]



Thienobenzothiepins like **2.70** have activity against *Aspergillus niger*.^[2.448]



Eberconazole **2.71** [128326-82-9] is presently undergoing clinical trials phase III as antimycotic. [2.449, 2.450]



High efficacy has been demonstrated in the clinic against tinea corporis and tinea cruris. Eberconazole and clotrimazole are inhibited by different components of *C. albicans* membrane protoplasts.[2.451]

3 1-(Mono-, di- and trihydroxyalkyl- and alkenyl)-1H-azoles, their thio analogs and derivatives

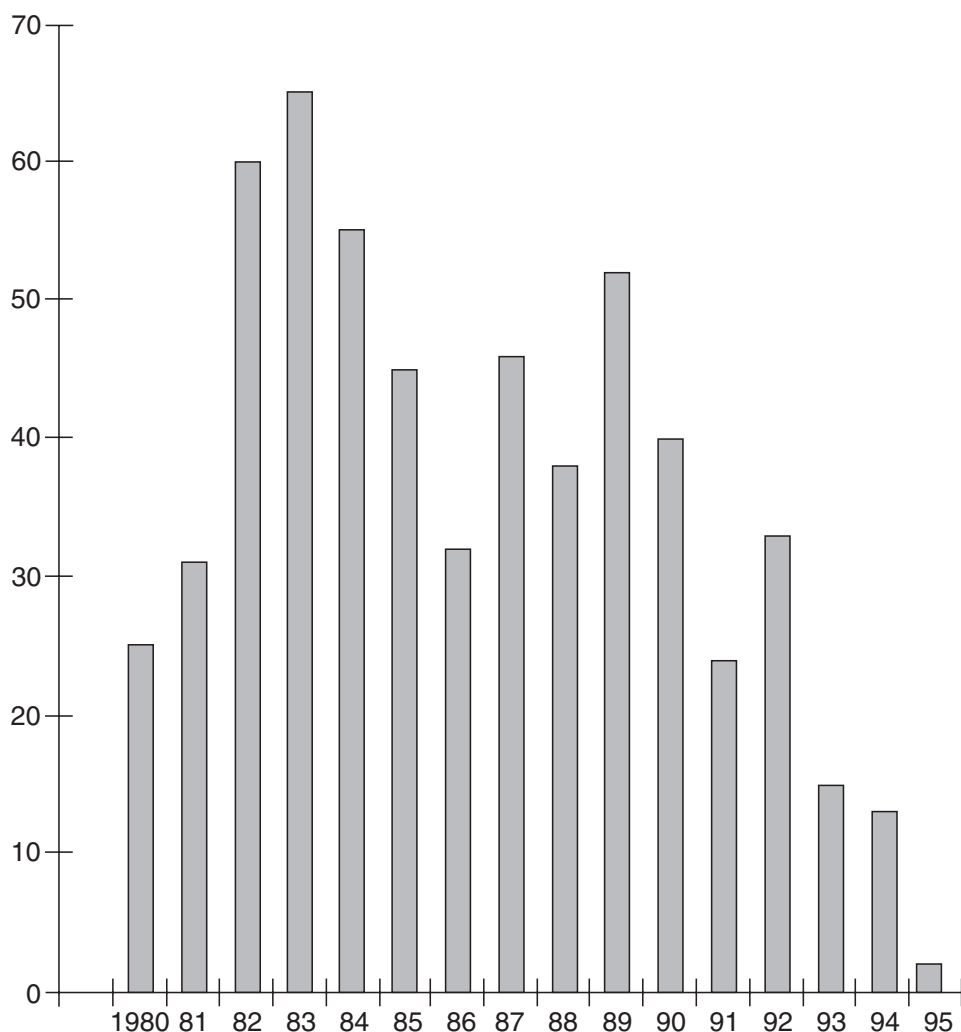
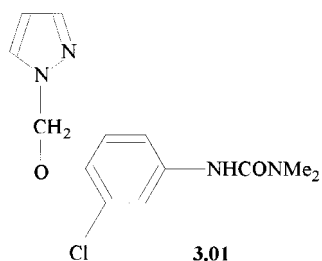


Fig. 3.1 Chronology of 576 patent applications of Chapter 3.

3.1 Derivatives of 1-(hydroxymethyl)-1H-azoles and their thio derivatives

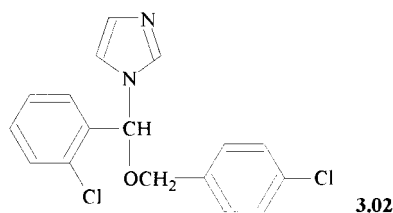
3.1.1 1-(Hydroxymethyl)-1H-pyrazoles and -imidazoles

Ether derivatives of the title compounds include 1-[(pyrazolylmethoxy)phenyl]ureas **3.01** which inhibit *Echinochloa crus-galli*. [3.001]

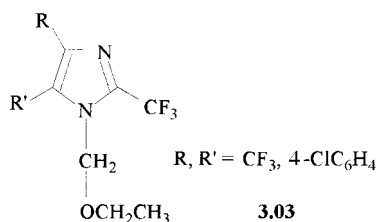


1-Pyrazolylmethoxy-iminoacetamides have been claimed as fungicides. [3.002]

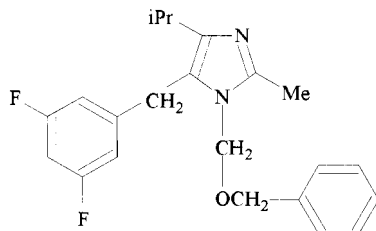
The preparation of 1-hydroxymethyl- and 1-alkoxymethyl-1H-imidazoles has been reviewed recently. [3.003] Imidazole derivative **3.02** shows antimicrobial activity similar to that of econazole and proved to be a cornerstone in the development of croconazole. [3.004]



1-Hydroxymethyl aryl-(trifluoromethyl)-(1H-imidazole ethers like **3.03** have been claimed as pesticides for their control of spider mites on *Phaseolus vulgaris*. [3.005]



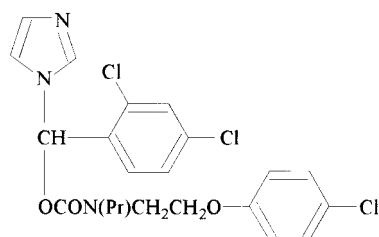
1-[1-(4-Chlorophenylthio)alkyl]imidazoles have been disclosed as inhibitors of *Helminthosporium teres* and *Erysiphe graminis* on barley.[3.006, 3.007] The benzylether **3.04** is endowed with high anti-HIV activity and reduced patient toxicity.[3.008]

**3.04**

Carboxylic acid esters derivatives of the title carbinols can be prepared from the corresponding acids and imidazolides.[3.009]

Imidazol-1-yl-carbamates have been claimed for their protection of barley against mildew.[3.010]

A prochloraz analog **3.05** shows high toxicity against *Penicillium italicum*. [3.011]

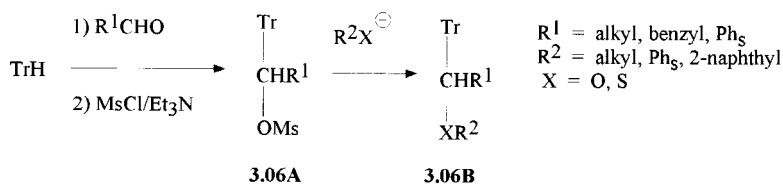
**3.05**

(For prochloraz, see section 5.4).

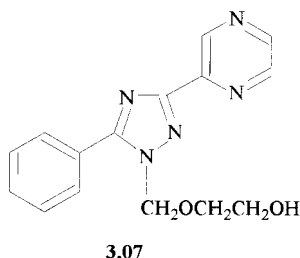
3.1.2 1-(Hydroxymethyl)-1H-triazoles, their ethers, oximino ethers and esters

1-Oxyalkylation of 1,2,4-triazoles has been briefly reviewed.[3.012] Some compounds with unsubstituted hydroxyl have been claimed as fungicides.[3.013, 3.014]

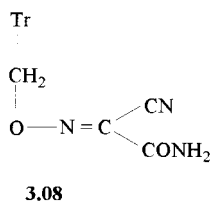
Ethers **3.06B** of the title compounds can be prepared from an aldehyde R^1CHO and mesyl chloride in the presence of triethylamine. The resulting mesylate **3.06A** reacts readily with alkoxides, aryloxides or their thiolate analogs to the desired ethers or thioethers **3.06B**. [3.012, 3.015, 3.016]



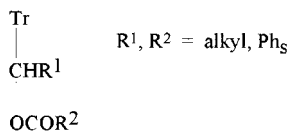
These compounds have been claimed as fungicides.[3.017, 3.018] Another example of **3.06B** with $\text{R}^1 = 6\text{-chlorobenzothiazol-2-yl}$, $\text{XR}^2 = 4\text{-chlorophenyl-}$ thio) shows good control of *Erysiphe graminis* on barley.[3.019] A further example **3.07** with $\text{XR}^2 = 2\text{-hydroxyethoxymethoxy}$ has antiviral activity.[3.020]



Oximinoethers such as **3.08** have been disclosed as fungicides.[3.021]



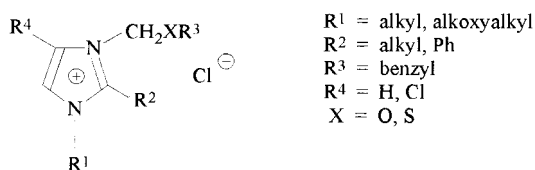
Esters **3.09** of the title compounds result from reaction of aldehydes R^1CHO and acid chlorides R^2COCl with triazole.[3.022]



Again the products disclosed possess fungicidal and bactericidal activity,[3.023] e.g. against *Fusarium vasinfectum* and *Rhizoctonia solani*,[3.024] and inhibit mildew on cucumber.[3.025]

3.1.3 1-Alkyloxymethyl- and 1-alkylthiomethyl-imidazolium compounds

Some imidazolium compounds have been discussed in section 2.4.2. The modification of title compounds **3.10** of the present chapter has been described in over 20 papers as disinfectants and microbicides also with anticorrosion and antistatic properties.



3.10

Substituents have been varied systematically as follows.[e.g. 3.026, 3.027, 3.028, 3.029, 3.030, 3.031, 3.032, 3.033, 3.034, 3.035, 3.036]

$R^1 = \text{H, Me to higher alkyl, CH}_2\text{OEt, CH}_2\text{OPr}$;

$R^2 = \text{H, Me, Et, Pr, i-Pr, Ph}$;

$R^3 = \text{CH}_2\text{OR, CH}_2\text{SR}$ ($R = \text{lower and higher alkyl, benzyl}$).

$R^4 = \text{H, Cl}$.

In vitro inhibition has been determined against Bacteria (*B. aeruginosa*, *P. vulgaris*, *E. coli*, *K. pneumoniae*, *Serratia marcescens*), cocci (*Staph. aureus*, *St. epidermidis*, *M. luteus*, *G. tetragena*, *Strep pyogenes*), fungi (*C. albicans*, *Rh. glutinis*) and *B. subtilis*, but no established standards were included in these tests. Compounds in Table 3.1 show optimal antifungal and antibacterial activity.

Table 3.1 Constant (underlined) and optimal variable (italicised) substituents for some series of quaternary imidazolium chlorides **3.10**, $R^4 = \underline{\text{H}}$.

Structure	R^1	R^2	R^3	Citation
3.10a	<u>Me</u>	<u>Me</u>	<i>CH₂SC₁₂H₂₅</i>	3.026
3.10b	<i>C₁₀H₂₁</i>	<u>H</u>	<i>CH₂OC₈H₁₇</i>	3.029
3.10c	<u>C₈H₁₇</u>	<u>C₆H₅</u>	<i>CH₂SC₈H₁₇</i>	3.034
3.10d	<i>C₁₂H₂₅</i>	<u>C₆H₅</u>	<i>CH₂SC₆H₁₃</i>	3.036

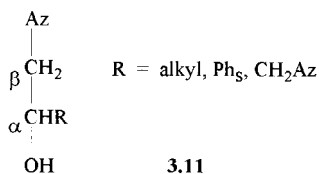
Some 264 of these quaternary imidazolium salts have been subjected to QSAR analysis in respect to their activity against *Pseudomonas aeruginosa* and *Escherichia coli*, using the rough sets method for activity.[3.037] A quantitative correlation has been found between minimum inhibition concentration (MIC), critical micelle concentration and hydrophobicity index.[3.037a]

To date, none of these compounds have reached the market.[3.038]

3.2 1-(2-Hydroxyalkyl)-1H-azoles

3.2.1 α -Substituted 1-(2-hydroxyalkyl)-1H-azoles

Title compounds of the general structure **3.11** can be prepared by sodium borohydride,[3.039] or, with high enantioselectivity, by microbial reduction [3.040] of the appropriate ketones $\text{AzCH}_2\text{C}(\text{O})\text{R}$.[3.041]



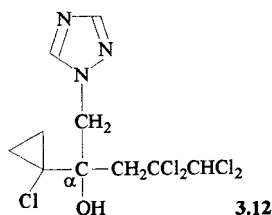
They can also be prepared by addition of aldehydes RCHO to 1-[(trimethylsilyl)methyl]-azoles.[3.042] These compounds with $\text{Az} = 1\text{-pyrazolyl, Im or Tr}$ have been claimed as fungicides.[3.043, 3.044, 3.045]. For example, one derivative with $\text{Az} = \text{Tr}$ and $\text{R} = 2,4\text{-Cl}_2\text{C}_6\text{H}_3$ controls barley net blotch, broad bean grey mold leaf spot, bean powdery mildew and grape downy mildew.[3.041] Other compounds with $\text{R} = 4\text{-ClC}_6\text{H}_4$ are weakly active against *Candida albicans* and with $\text{Az} = \text{Tri}$, moderately active against *Candida* sp. (*C. glabrata*, *C. tropicalis*, *C. guillermoidii*, *C. krusei*, *C. parapsilosis*, *C. lipolytica*).[3.046] Another similar substance with $\text{Az} = \text{Tr}$, $\text{R} = 4\text{-(bromophenoxy)-2-chlorophenyl}$ controls *Venturia inaequalis* and *Erysiphe graminis*. [3.047]

3.2.2 α,α -Disubstituted 1-(2-hydroxyalkyl)-1-H-azoles

Synthetic strategy and synthetic procedures have been reviewed recently.[3.048ff]

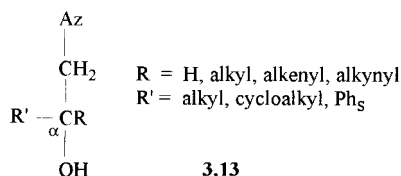
3.2.2.1 α,α -Di(halogenalkyl) 1-(2-hydroxyalkyl)-1H-azoles

Title compounds with additional halogen on the alkyl have been claimed as agrochemical fungicides.[3.049, 3.050, 3.051] A typical substance **3.12** shows superior activity against *Botrytis cinerea* on beans.



3.2.2.2 α -Alkyl, cycloalkyl, alkenyl and halogenoalkyl-, α -aryl or heteroaryl-1-(2-hydroxyalkyl)-1H-azoles

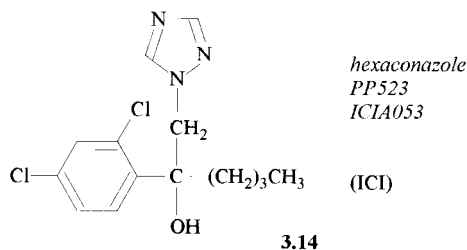
A large number of patent applications have been filed, and some original papers appeared, for compounds of the general structure **3.13**. [3.052, 3.053, 3.054, 3.055, 3.056, 3.057, 3.058, 3.059]



A QSAR study has been reported of 2-alkyl, -alkenyl, and -cyclopropylalkyl)-2-(2,4-dichlorophenyl)-2-hydroxy 1-imidazole with antifungal activity against *Candida* spp., *Aspergillus*, and dermatophytes at ideal lipophilicities (log P₀) for each group of fungi. [3.060] This is interpreted as a consequence of membrane perturbation of the fungus by the ionized and/or non-ionized imidazole compound, possibly via inhibition of membrane-bound enzymes.

From these, hexaconazole, UK, and UK-46,245 have been studied more closely. [3.061]

Hexaconazole **3.14**, [79983-71-4] has been resolved; its main antifungal activity rests in the (–)-enantiomer. [3.048]

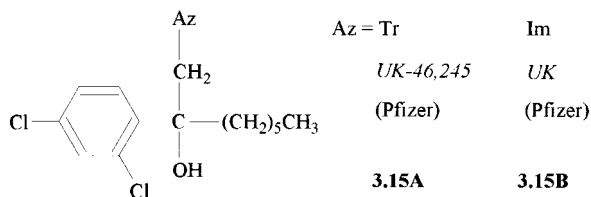


The agent protects and eradicates a broad range of fungi, especially Basidiomycetes and Ascomycetes. [3.061]

Hexaconazole controls *Podosphaera leucotricha*, *Gymnosporangium juniperi-virginianae* and *Venturia inaequalis* on apples, *Guignardia bidwellii* and *Uncinula necator* on vines, *Hemileia vastatrix* on coffee and *Cercospora* spp. on peanuts, rusts, mildew and eyespot on wheat, fungal pests on bananas, peaches, vegetables, citrus and soft fruit. [3.061, 3.062, 3.063, 3.064] Hexaconazole controls powdery mildew on vine and apple, black rot and apple scab. [3.065] It also inhibits *Puccinia horiana* on chrysanthemum and *Sphaerotheca pannosa* on roses. [3.066]

A time-limited tolerance for residues of hexaconazole has been identified. [3.067] The agent has been recommended as a fungicidal wood preservative. [3.068]

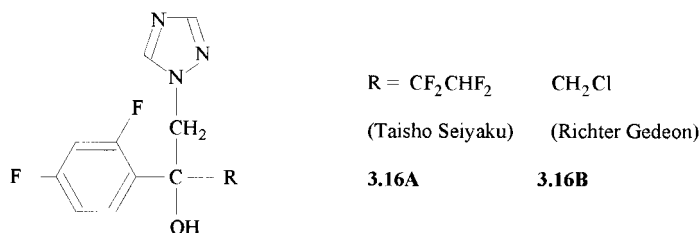
Compound UK-46,245, **3.15A** has been used as a corner-stone in the structural development which resulted in fluconazole.[3.069]



It shows high inhibition of the metabolism of testosterone hydroxylations catalyzed by mouse hepatic microsomal cytochrome P-450.[3.070]

A closely related experimental fungicide is the imidazole analog UK, **3.15B** which shows more selectivity of mouse P-450 cytochrome than fluconazole.[3.071]

Compound **3.16A** displays good activity against *A. fumigatus* and is more effective than fluconazole against systemic candidiasis in mice.[3.072, 3.073, 3.074]



Substance **3.16B** seems very promising from the *in vitro* antifungal data.[3.073, 3.074]

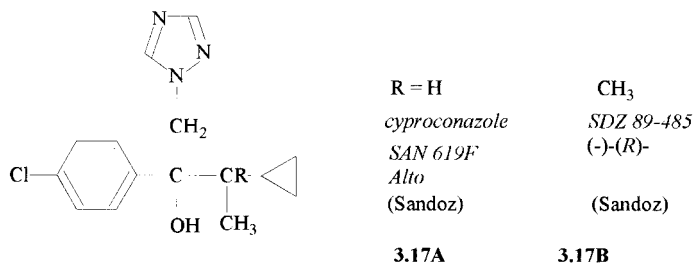
A number compounds with the general structure **3.13** but with R = alkenyl or halogenoalkenyl, show good activity against *P. recondita*, *C. arachidocola*, *B. cinerea*, *E. graminis* and *R. solani*. [3.052, 3.075, 3.076, 3.077, 3.078, 3.079]

Further compounds **3.13** with R = halogenoalkyl inhibit *Candida* infection in mice, protect wheat against *Puzinia graminis*, and control *Piricularia orycae* and *Erysiphe graminis hordei* on barley.[3.080, 3.081, 3.082, 3.083, 3.084]

Other substances **3.13** with R = cyclopropylalkyl or halogenocyclopropyl also inhibit *Candida albicans* infection in mice.[3.085, 3.086, 3.087] Their control of *Erysiphe graminis tritici* on wheat is enhanced by alkoxylates.[3.088, 3.089, 3.090] They are toxic to *Pseudocercospora herpotrichoides*, [3.091] and *Eutrypa lata* on pruning grapes.[3.092]

From these, antifungal agents cyproconazole **3.17A**, [R*,R*-diastereoisomer 94361-06-5] [3.093, 3.094] and SDZ-89-485, **3.17B** have emerged.

Inhibition of cyproconazole against *Candida albicans* infection in mice is located in the (–)-isomer,[3.087] however, against a number of pathogenic plant fungi the *in vitro* and *in vivo* activities are highest with a 1:1:1 mixture compared with any of the single enantiomers (+), (–), A and B.[3.095] Thus, cuproconazole promises to be an outstanding agent in terms of overall performance and decreased risk.



The agent penetrates into plant tissue, and is translocated acropetally with long-lasting preventive and curative activity.[3.096] It controls powdery mildew and *B. cinerea* on grape,[3.097] and is generally active against rusts and septoria, and decreases eyespot.[3.098]

In seed dressing formulations, rose bengal reduces phytotoxicity of cyproconazole.[3.099]

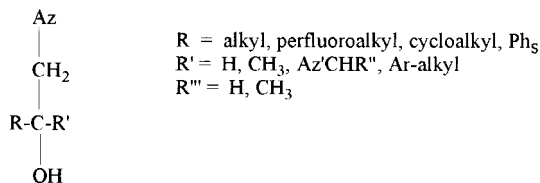
Cyproconazole is recommended as an industrial microbicide for the protection of wood, coatings, leather and paper.[3.100, 3.101]

SDZ-89-485, **3.17B** [103183-65-9] as (-)-(R)-enantiomer has been designed as an antimycotic with superior selectivity for the target enzyme of fungal sterol biosynthesis.[3.102, 3.103] It is superior to standard antimycotics against rodent candidosis and also has superior oral activity against murine systemic candidosis, systemic infection by *Histoplasma capsulatum*, *Sporothrix schenckii* and *Coccidioides immitis*. It shows only weak or moderate interactions with cytochrome P-450 isolated from adrenal glands, testes and placenta. Even so, the development of SDZ-89-485 had to be discontinued.[3.104]

Compounds related to **3.13** with R' = 3-phenylisoxazol-5-yl control *Erysiphe graminis*. [3.105]

3.2.2.3 α -Alkyl-, α -arylmethyl- and α -heterocyclylmethyl-1-(2-hydroxyalkyl)-1H-azoles

Title substances **3.18** with Az = Tr and R = perfluoroalkyl show anti-leishmanial activity. [3.106]



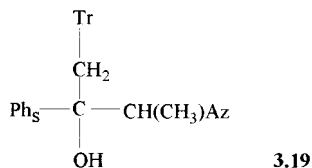
3.18

Stereocontrolled synthesis has been described. [3.107]

Many claims include Ar = Ph_s and a cyclopropyl or chlorocyclopropyl group connected to substituent R.[3.108, 3.109, 3.110, 3.111, 3.112, 3.113, 3.114, 3.115,

3.116, 3.117, 3.118, 3.119, 3.120] These substances inhibit *Candida* infection in mice, *Pyricularia oryzae* on rice, *Uncinula necator* on grapes, *Erysiphe graminis hordei* on barley, *Pellicularia sasakii* on rice, and *Venturia inaequalis*.

From the title compounds, series **3.19** in their (2*R*,3*R*)-stereoform exert a strong and selective inhibitory effect on the sterol synthesis of *C. albicans* when compared with that in the rat liver.[3.121]

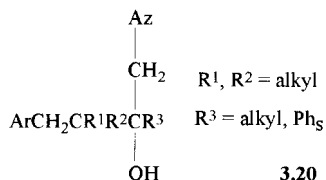


In another claim, the cyclopropyl group has been expanded to cyclopentyl or cyclohexyl.[3.123]

Compounds **3.18** with Ar = thiazol-2-yl display high p.o. efficacy against candidiasis of mice,[3.124], and others with Ar = quinol-2-yl show high toxicity against *Cryptococcus neoformans*. [3.125]

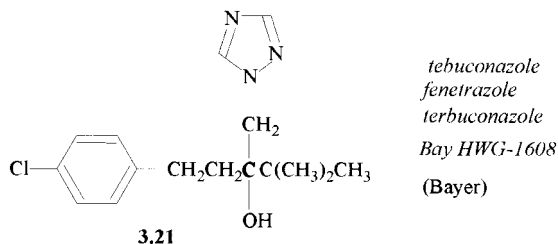
3.2.2.4 α -Alkyl- or -aryl-, α -(2-arylethyl)1-(2-hydroxyalkyl) azoles and unsaturated analogs

Title compounds with the general structure **3.30** have been claimed as fungicides for their activity against *Candida albicans*,[3.126, 3.127, 3.128, 3.129, 3.130, 3.131, 3.132, 3.133] and *Pyricularia oryzae* on wheat.[3.134, 3.135, 3.136]



Synthetic aspects have been reported.[3.059]

Tebuconazole **3.21** [107534-96-3] has been developed from these series as a seed and foliar fungicide with systemic action.[3.093, 3.137, 3.138, 3.139]



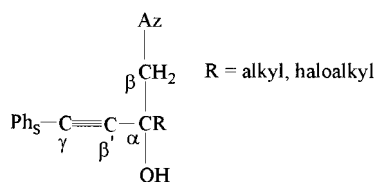
The chemistry and biochemistry of tebuconazole has been reviewed.[3.140, 3.141] A second site of action besides 14 α -demethylase was postulated but has been ruled out by later work.[3.142] Tebuconazoles antimicrobial activity rests mainly within the (–)-S-enantiomer; however *in vitro* activity against resistant strains of *S. lipolytica* and *P. oryzae* is controlled by the (+)-form.[3.140, 3.143]

In formulations of tebuconazole, cyclic imides, carbamates, carboxamides and urea lactams have been suggested as crystallization inhibitors.[3.144, 3.145, 3.146, 3.147, 3.148] Dioctyl sebacate increases storage stability and fungicidal effect.[3.149]

Tebuconazole has been used successfully against *Ustilago*, *Tilletia*, *Fusarium*, *Septoria*, *Pyrenophora*, *Cochliobolus*, rusts and powdery mildew. It is effective against *Mycosphaerella* on bananas and *Botrytis cinerea* on grapes.[3.150] It combats *Pseudocercospora herpotrichoides* on wheat and barley,[3.151] *Onobasidium theobromae* on cocoa,[3.152] *Cercosporida* on peanuts,[3.153] *Sclerotium cepivorum* of onion,[3.154] *Blumeriella jaapii* on sour prunes,[3.155] and *Alternaria macrospora* on cotton,[3.156] and several diseases of oilseed rape.[3.157] The control of *Erysiphe graminis tritici* on wheat is enhanced by aliphatic alkoxylates.[3.158]

Tebucobazole is marketed as wood fungicide Preventol A8 and recommended for the protection of other materials against *Sclerophoma pityophila*, *Hylotrupes bajulus* and *Aspergillus niger*.[3.159, 3.160, 3.161] Environmental hazards have been discussed recently in face of the toxicity to algae, daphnie, and trout hatch.[3.162]

Related structures **3.22** may have a double or triple bond between β' -C and γ' -C,[3.163] or these carbon atoms together can be part of a cyclopropane ring, a structural variation successful in the cyproconazole series (see section 3.2.2.3). [3.164, 3.165, 3.166]



3.22

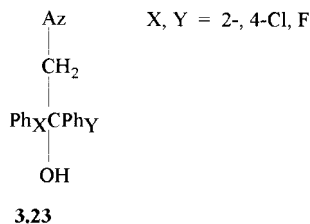
For some of these compounds, inhibition of *Botrytis cinerea* on paprika and on tomato plants has been demonstrated.[3.165, 3.166]

3.2.2.5 α,α -Diaryl-1-(2-hydroxyalkyl)-1H-azoles and related heteroaryl compounds

Title compounds **3.23** have been claimed as fungicides.[3.167, 3.168, 3.169, 3.170]

Synthetic aspects have been studied.[3.059]

Under basic conditions or high temperatures, products with Az = 1,2,4-triazol-4-yl can arrange to 1,2,4-triazol-1-yl and vice versa.[3.171]

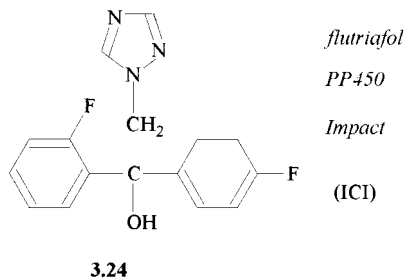


Title compounds inhibit, especially as (–)-enantiomers, *Candida albicans*, [3.170] and *Puccinia recondita* on wheat. [3.168] A series of 34 of these substances have been analyzed by Automated Structure Evaluation (Multi-CASE) for *in vitro* activity against *C. albicans*, teratogenicity, and therapeutic index. [3.172] Typical fragments, anti-*Candida* biophores and teratogenic biophores have been identified.

Some title compounds are also endowed with antiviral activity against herpes, varicella, mononucleosis, pseudorabies and cytomegalovirus in humans, cattle, pigs and poultry. [3.169] Out of five substituent combinations X/Y [3.23, A) flutriafol, see below; B) X/Y = 2-Cl/4-F; C) 2-Cl/4-Cl; D) 4-F/4-F; E) 4-Cl/4-F] the *in vitro* ED₅₀ against *U. maydis* showed highest activity of compound B, with an optimal factor of 4,4-dimethyl to 4-desmethyl sterols for derivative D. [3.173]

In these series, agents flutriafol, ICI-153,066 and ICI 159,265 have been thoroughly investigated.

Flutriafol **3.24**, [87676-93-5; 76674-21-0] is a systemic fungicide which controls *Erysiphe graminis*, *Puccinia* spp., *Septoria* spp., *Helminthosporium* spp., *Rhynchosporium secalis*, and soil- and seed-borne foliar diseases caused by fungi. [3.093, 3.174, 3.175]

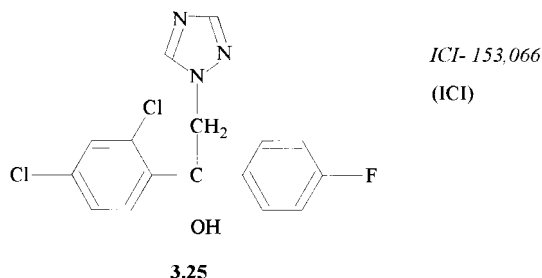


Protectant activity against wheat rust and against mildew on apple has been plotted versus log P of aromatic substituents in a series of flutriafol derivatives. [3.093] It is recommended against *Sphacelotheca reiliana* of corn. [3.176]

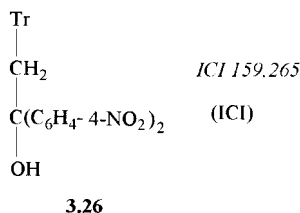
Flutriafol has been resolved to find its main antifungal activity in the (–)-enantiomer. [3.048]

Agent ICI-153,066, **3.25**, [76674-22-1] has been found *in vitro* superior to ketoconazole against *Zygomycetes* spp. and *Torulopsis glabrata*. [3.177]

In vivo, this agent is 10–100 times superior against vaginal candidiasis in rodents and coccidiomycosis in murines. [3.177] It inhibits *Trichophyton quinckeanum* and prevents *Cryptococcus neoformans* infection in mice. [3.178, 3.179]



However, ICI-153,066 is teratogenic and embryotoxic in the rat and has been suspended.[3.172, 3.180] Out of several substituent combinations X/Y of structure **3.23**, the lowest teratogenic hazard is associated with X = Y = 4-CF₃, -CN, -NO₂, i.e. in compound **3.26**. [3.180, 3.181]

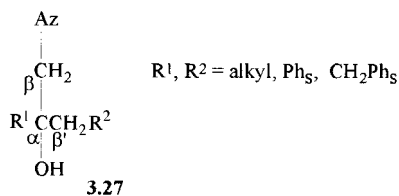


The relation between antifungal potency and teratogenicity has been tested by Multiple-Computer-Automated Structure Evaluation (Multi-CASE) which arrived at an *a priori* prediction of the toxicity of ICI 153 066.[3.172]

Heterocyclic analogs of **3.23** with Ph_Y = subst. isoxazolyl,[3.182] thiazolyl,[3.183, 3.184, 3.185, 3.186] or pyridyl,[3.187, 3.188, 3.189] show activity against *Candida albicans*.

3.2.2.6 α-Aryl-α-arylmethyl-1-(2-hydroxyalkyl)-1H-azoles

Title compounds **3.27** have been claimed as antimycotics and fungicides.[3.190, 3.191, 3.192]



In one disclosure, activity against *Trypanosoma cruzi*, the causative agent of Chagas' disease, has been demonstrated.[3.192] The β'-carbon can be substituted with halogen,[3.191, 3.193, 3.194], or with alkyl.[3.192, 3.193, 3.194, 3.195, 3.196, 3.197, 3.198, 3.199, 3.200, 3.201, 3.202, 3.203, 3.204, 3.205] The same carbon atom can also be part of a cyclopropane,[3.185, 3.197, 3.207, 3.208, 3.209, 3.210] or of a

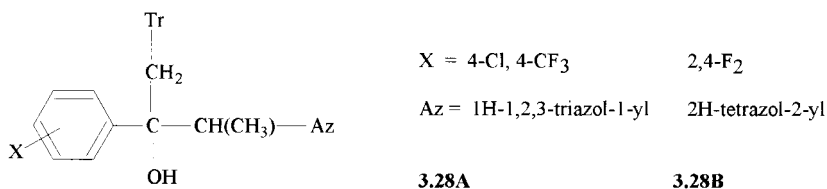
cyclobutane ring.[3.211] Saccharin adducts seem to improve the protective action of these type of compounds against *Pyricularia oryzae* on rice, *Erysiphe graminis hordei* and *Venturia inaequalis*. [3.210] For many representatives of these structures, excellent inhibition of *Candida albicans* infection in mice has been demonstrated.

3.2.2.7 α -Aryl- α -heterocyclymethyl-1-(2-hydroxyalkyl)-1H-azoles

A further set of variations of structures **3.27** is based on the replacement of R^1 or R^2 by heterocycles. As such, R^1 can be replaced by thienyl.[3.212]

R^2 may be a five- or six-membered heterocycle, such as 1-pyrrolyl, which might be further substituted with styryl,[3.213] 1-pyrazolyl,[3.214] 2-oxazolyl,[3.196] isoxazolyl,[3.197] imidazolyl,[3.198] 1,3-dioxanyl,[3.199] pyridinyl,[3.191, 3.200, 3.201] pyrimidinyl,[3.200, 3.201] pyridazinyl,[3.201] or triazinyl.[3.201]

The most important variety however have been compounds with R^2 = imidazolyl,[3.202, 3.215] (which might be further substituted,[3.216]), 1,2,3-triazol-1- or 2-yl-, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, and tetrazol-1-, 2- or 5-yl.[3.217, 3.218, 3.219, 3.220, 3.221, 3.222, 3.223] Optimal representatives of these series, which *in vitro* and *in vivo* are superior to fluconazole against *C. albicans*, are represented by **3.28A** and **3.28B**. [3.223]



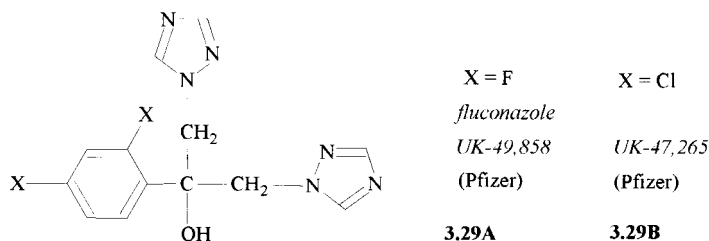
Placing 1,2,4-triazol-1-yl for R^2 in **3.27** produces the fluconazole family of compounds in which the teratogenic hazard is reduced by a factor of 6–12.[3.181, 3.224] A series of 34 of these triazoles has been studied by Multi-CASE methodology, and anti-*Candida* biophores and teratogenic biophobes identified as structural fragments.[3.172] Variation of substituents X in formula **3.29A** has resulted in 2H/4-CF₃ and 2F/4-CF₃ for lowest teratogenic hazard to the rat embryo.[3.181, 3.224]

The triazole of substituent R^2 can be further substituted with chlorine,[3.209], alkyl, alkenyl, heterocyclyl,[3.203, 3.225] or styryl.[3.226]

From the series above, fluconazole, ICI 195,739 and D-0870 have been developed.[3.227, 3.228, 3.229, 3.230, 3.231, 3.232, 3.233, 3.234, 3.235, 3.236, 3.237]

3.2.2.8 Fluconazole: Development strategy, pharmaceutical and pharmacokinetic aspects

Fluconazole **3.29A**, [86386-73-4] appears to be the most successful azole antimycotic developed in the past 15 years.[3.238, 3.239]



It tops a list of \$1–2 billion projected sales for 2000.[3.240] New synthetic methods have been evaluated.[3.241, 3.242]

The structural development of what was to become fluconazole has been envisioned as antimycotic of good safety, effective both p.o. and i.v., with wide spectrum of activity and suitable not only for treatment but also for the prophylaxis of fungal infections. Since most azole antimycotics known so far had been rapidly and extensively metabolized, the drug of choice should not suffer along the path of p.o. doses—absorption in the gastrointestinal tract—passage through the liver—and delivery to the site of action. In addition, complexing with protein, as a result of high lipophilicity, should not be prominent.[3.238, 3.243]

To achieve this goal, tertiary alcohols have been selected as a starting group since they had the highest potential of good *in vivo* activity, in preference to tetrahydrofurans, dithiolanes and dioxolanes, though they still were easily metabolized.[3.243] 1,2,4-Triazoles have then been preferred to imidazoles. Their greater *in vivo* activity suggested that at least one site of the molecule had been blocked against metabolism; also they show greater selectivity towards fungal cytochrome P-450 enzyme and do not affect mammalian testosterone synthesis.

The exchange of hexyl in compound **3.15A**,[3.069] an important cornerstone of structural development (see section 3.2.2.2) by CH₂-Tr has resulted in compound **3.29B** which is 100-fold as potent *in vivo* against systemic candidiasis than ketconazole.[3.243]

Variation of the phenyl substituents X brought an optimal example with 2,4-F₂ after comparison of water solubility, long half-life, and high urinary recovery (clearance without metabolism). Thus, fluconazole was born.[3.244, 3.245]

The replacement of imidazole by triazole, the introduction of a second triazole group, and the replacement of the 2,4-dichlorophenyl substituent characteristic of many earlier antimycotic agents by 2,4-difluorophenyl have thus resulted in a marked decrease in lipophilicity and metabolic vulnerability of fluconazole.[3.246] Its solubility in water may reach 6 g/L.[3.247] Consequently, fluconazole is absorbed quantitatively from the gut, with absorption being independent of gastric acidity or food intake. The drug is distributed in all body water passing CNS, CSF or ocular barriers, and accumulated in skin and nails.[3.247] Flucon-

azole is excreted mainly in urine and unchanged, and its half-life of 30—36 hours permits a one doses/day regimen.

Fluconazole is involved in fewer inter-drug reactions than ketoconazole and itraconazole, which might be important for patients with altered pharmacokinetics.[3.248]

A crystalline monohydrate of fluconazole has been prepared, and its conformation calculated. It has been found less bitter than the non-hydrated agent.[3.249, 3.250] Parenteral and suppository formulations have been elucidated.[3.194, 3.251] In general, formulation is less of a problem compared with other azole antifungals with very low aqueous solubility (see section 2.10.1).[3.252]

The pharmacology, pharmacokinetics and indications of fluconazole have been summarized,[3.246, 3.247, 3.253, 3.254, 3.255, 3.256, 3.257] and presented in a symposium report.[3.258] The drug is strictly fungistatic.[3.259]

3.2.2.9 Fluconazole: Preclinical and clinical aspects, resistance.

Fluconazole is *in vitro* significantly more toxic to *C. albicans* than to dermatophytes like *T. rubrum*, *T. mentagrophytes*, *M. canis* and *E. floccosum*. [3.260] In contrast, this drug is a much weaker inhibitor of *C. krusei* than ketoconazole or itraconazole, this is believed to result from a much lower intracellular accumulation.[3.261]

Fluconazole is 5-to20-fold more active than ketoconazole against *Aspergillus* and *Cryptococcus* infections in mice.[3.262] The high blood levels allow a single effective doses in the treatment of vaginal and mucocutaneous candidiasis. [3.263, 3.264] An excellent safety profile and good tolerance permit high doses in late-stage AIDS patients against cryptococcal and coccidioidal meningitis,[3.243, 3.244, 3.264] against extraneural coccidioidal infection, chronic disseminated candidiasis,[3.264] against oropharyngeal candidiasis,[3.265, 3.266] against candidal esophagitis,[3.267] against histoplasmosis,[3.268] and against lymphocutaneous sporotrichosis.[3.269]

Non-*albicans* spp. such as *C. glabrata* are intrinsically more resistant to fluconazole, and infections by these fungi seem to be on the increase in hospitals.[3.264] Generally, resistance against fluconazole has developed more frequently than against ketoconazole and itraconazole.[3.256, 3.266, 3.270, 3.271, 3.272] Multidrug transporters (ATP-binding cassettes) seem to be involved in the formation of this resistance.[3.273]

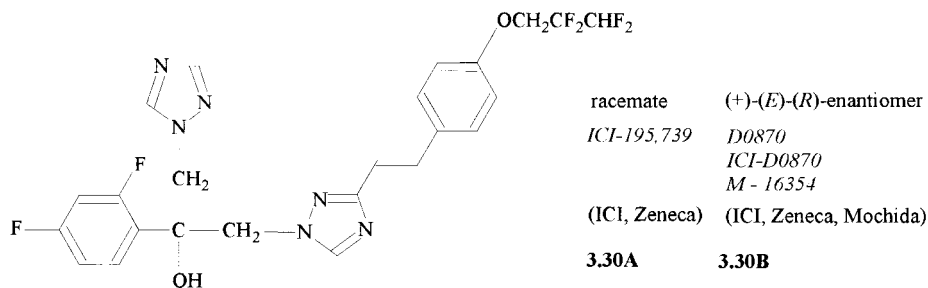
This might become a problem in the important, often very long prophylactic use of fluconazole in immunocompromised patients. Resistance to fluconazole is now considered so serious in a very recent discussion of present research efforts, that new antimycotics are qualified by the inhibition of fluconazole-resistant strains of *C. albicans*, *C. krusei* and *A. fumigatus*. [3.273a]

Fluconazole presents an excellent ocular profile which might be useful as an orally administered agent in ocular fungal infections.[3.274, 3.275]

Alopecia appears to be a common adverse event when higher doses of fluconazole have been used for two months and longer.[3.276]

3.2.2.10 Close relatives of fluconazole

Compound **3.30A**, ICI 195,739 [103961-78-0] has been developed from compound **3.25**, ICI 153,066 (see section 3.2.2.5).[3.277]



The strategy followed in the development of ICI 195,739 has been the assessment of oral efficacy in the mouse, then against vaginal infection with *Candida albicans* in the rat, studies of rat pharmacology and teratology, and testing for inhibition of aromatase. As some 3-substituents such as halogen and phenylethyl on the second triazole have been found to increase potency, changing to p-substituted (Z)-styryl, suggested by computer graphics, further increased *in vitro* potency by 2–3 orders of magnitude. (In other azole series, styryl groups have been used with success, see section 2.9.2) Further optimization of the p-substituent improved *in vivo* activity by slowing down metabolic degradation and thus agent ICI-195,739, **3.30A** has been produced.

A radiolabeled form of ICI 195,739 has been prepared.[3.122]

ICI 195,739 shows 10–100 times the potency of ketoconazole, with good p.o. activity against vaginal candidosis in mice and rats and against dermatophytic lesions in mice and guinea pig, but with intolerable toxicity in rat, rabbit and dog.[3.277, 3.278]

Although activity against mammalian aromatase (and thus potential reproductive toxicology) could be lowered by a factor of 8 using the (R)-(-)-enantiomer, teratogenic malformations have still been seen.

ICI 195,739 is freely permeable through the fungal cell walls, as experiments with whole and broken cells have shown.[3.279] Compared with fluconazole, the minimum effective oral doses of this agent is lower by a factor of 5–10 against *C. albicans* and *T. quinckeanum* in mice, and against rodent vaginitis models.[3.280] Its activity against *Blastomyces dermatitis* in mice is 50 times higher than that of ketoconazole, with curing of murine pulmonary blastomycosis.[3.281] ICI 195,739 cures well-established *Trypanosoma cruzii* infections in mice at doses of 10 mg/kg/day for 5–6 weeks, operating by a second mechanism in addition to the blockade of sterol biosynthesis.[3.280, 3.282]

Compared with fluconazole, ICI 195,739 is several fold more potent in experimental fungal diseases. A high serum concentration of about 20 mg/mL is achieved with long half-life (48 h). *Fungicidal* (in contrast to fungistatic) activity in experimental systemic blastomycosis has been observed.[3.283]

Antimycotic agent D-0870 or DO870, **3.30B** [149715-95-7; 141113-28-2; sulfate 141113-29-3] represents the (*R*)-(+)-enantiomer of ICI 195,739, which has been found to be the center of antimicrobial *in vitro* and *in vivo* activity. [3.284]

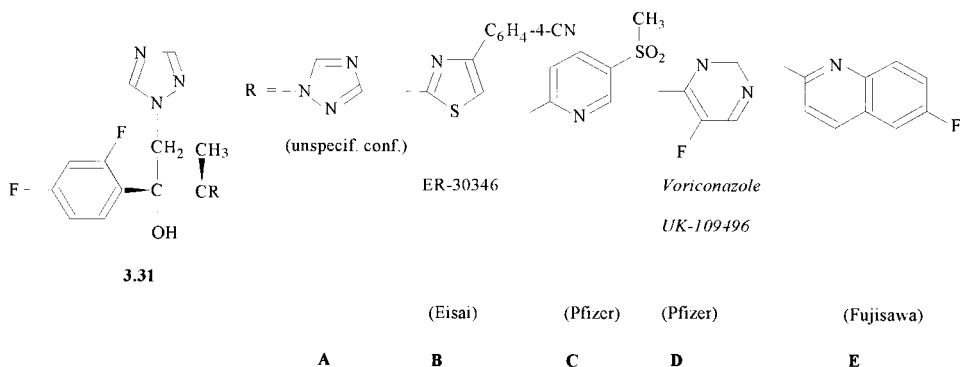
Oustanding *in vitro* inhibition of fluconazole-resistant strains of *C. albicans* and of *C. neoformans* has been demonstrated.[3.273a, 3.286] D0870 is also active against *Trichosporon beigelii* in immunocompromized mice. *In vivo* activities in normal and in immunocompromized mice against infections by *C. albicans*, *C. neoformans*, and *A. fumigatus* are superior by a factor of 2–90 to fluconazole, and of the same order of magnitude in the two animal groups, while fluconazoles action is remarkably attenuated in the second animal group.[3.285, 3.286] D-0870 inhibits more than half of *C. albicans* isolates which have drawn attention because of their elevated fluconazole and itraconazole MICs.[3.287] Thus, it has potential for the therapy of infections caused by fluconazole-resistant *Candida* spp.[3.288] In a similar therapeutic situation, D0870 is superior against *C. lusitaniae* and *T. beigelii*. [3.289]

D0870 has some efficacy in the treatment of invasive aspergillosis, as demonstrated in the neurotropic mouse respiratory model.[3.290]

It has been demonstrated in the mouse, that D0870 may be useful in the treatment of long-term Chagas disease, a condition which is currently incurable.[3.291, 3.292]

3.2.2.11 α -Aryl- α -heterocyclalkyl-1-(2-hydroxyalkyl)-1H-azoles; further relatives of fluconazole

Replacement of the second triazolylmethyl in fluconazole by 5-fluoro-pyrimidine-4-yl and inserting an α -methyl have resulted in voriconazole **3.31D**, [137234-62-9], an orally active broad-spectrum antimycotic.[3.293, 3.300]



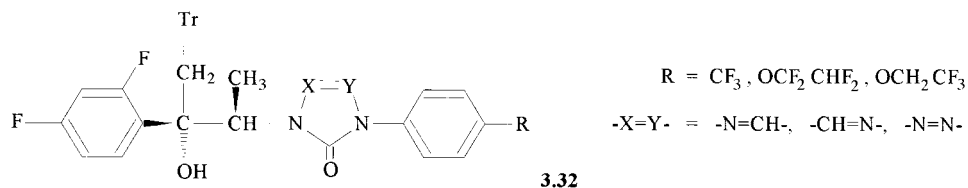
In vivo efficacy of voriconazole against systemic *C. albicans* and pulmonary *Cryptococcus neoformans* infections has been found comparable with that of fluconazole and itraconazole, but has proved superior against systemic candidiasis caused by *C. krusei*, *C. glabrata* and azole-resistant *C. albicans* spp. and against

invasive aspergillosis in rabbits and guinea pigs.[3.273a, 3.294, 3.300] Clinical observations indicate efficacy against oropharyngeal candidiasis in immunocompromized patients, and against acute invasive and chronic aspergillosis in neutrotropic patients.

In a number of compounds similar to voriconazole, the pyrimidyl has been replaced by 1,2,4-triazol-1-yl to give **3.31A**, [3.273a, 1.22] which shows high activity against *Aspergillus* spp., or by thiazol-2-yl to give **3.31B**, ER-30346 with demonstrated superiority or equality to itraconazole and fluconazole against systemic infection by *C. albicans*, *C. neoformans*, and *A. fumigatus*, against pulmonary aspergillosis, candidiasis, and cryptococcosis, against intercranial cryptococcosis (all in mice) and against oral candidiasis in rats.[3.124, 3.273a, 3.296, 3.297] ER-30346 shows good oral availability and does not influence pentobarbital sleeping time.

Similarly, pyrimidyl in voriconazole has been replaced by pyridin-2-yl to result in **3.31C**, which is distinguished by excellent activity against cranial cryptococcosis and low hepatic toxicity in rats.[3.189, 3.273a] Replacement of the pyrimidyl in voriconazole **3.31D** by chinolin-2-yl produces compound **3.31E**, also characterized by inhibition of *Cryptococcus neoformans*. [3.273a]

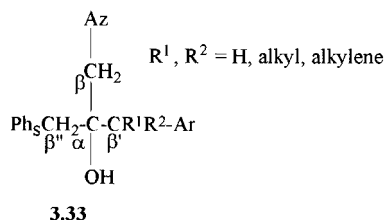
Further, replacing the pyrimidyl in voriconazole by triazolones yields voriconazole analogs **3.32** with potent *in vivo* antifungal activity.[3.297, 3.298, 3.299]



Among these, a substance with R = OCH₂CF₂CHF₂ and -N=CH- for -X=Y-, shows excellent efficacy against systemic candidiasis in mice.[3.273a]

3.2.2.12 α -Bis-arylalkyl-1-(2-hydroxyalkyl)-1H-azoles and heteroaryl analogs

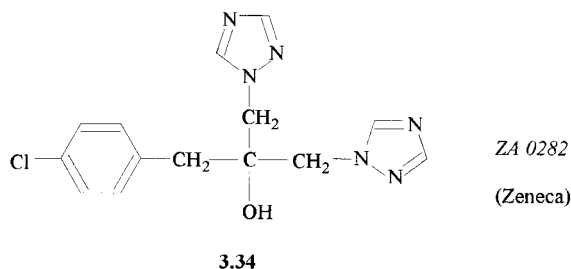
Title compounds **3.33** can be substituted at β'' -Cor this carbon can be part of a cycloalkane ring.



Ar denotes an aromatic or heterocyclic ring such as pyrazole, imidazole, dioxolane, dioxane or 1,2,4-triazole.[3.301, 3.302, 3.303, 3.304, 3.305, 3.306]

In vitro activities have been demonstrated for these compounds against *Trichophyton mentagrophytes*, *in vivo* against *Candida albicans* infection in mice, against *Cichliobolus sativus* and *Erysiphe graminis* on barley, *Puccinia recondita* on wheat, *Sphaerotheca fuliginea* on cucumber and *Venturia inaequalis* on apple.

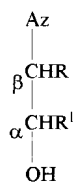
Compound **3.34**, ZA0282 seems to have been of particular interest as fungicide; a ^{14}C -labeled form has been prepared.[3.122]



3.2.3 α,β -Disubstituted 1-(2-hydroxyalkyl)- 1H-azoles

3.2.3.1 α -Alkyl-, β -(alkyl, aryl- or aralkyl)-1-(2-hydroxyalkyl)-1H-azoles

Title compounds **3.35** with α -alkyl, β -alkenyl, haloalkyl or cycloalkyl substitution have been claimed as fungicides with activity against *Puccinia graminis* on wheat and cucumber mildew.[3.307, 3.308, 3.309, 3.310].

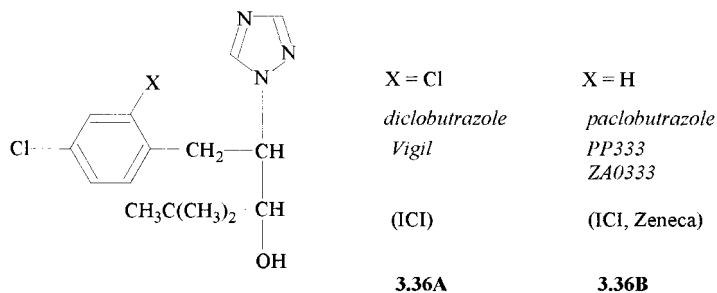


3.35

α -Alkyl- β -aryl or -aralkyl title substances can be prepared by diastereoselective reduction of the respective ketones with $\text{TiCl}_4\text{-n-Bu}_4\text{NBH}_4$. [3.311] They have been claimed as antimycotics and fungicides with activity against *Erysiphe cichoracearum* on cucumber, *Pyricularia oryzae*, *Leptosphaeria nodorum* and *Sphaerotheca fuliginea*. [3.312, 3.313, 3.314, 3.315, 3.316, 3.317, 3.318, 3.319, 3.320, 3.321, 3.322, 3.323] From these series, diclobutrazol and paclobutrazole have been developed.

Diclobutrazol **3.36B**, [75736-33-3] a systemic fungicide with its main activity residing in the 2R,3R-enantiomer,[3.093, 3.324, 3.325] is transformed by UV light into the s-triazolo[5,1a]isoquinoline ring system.[3.326]

The preferred solution conformer is similar to the crystal conformer.[3.327] Enantiomers have been separated by chiral derivatization and gas chromatography.[3.328]



Diclobutrazole inhibits *Rhynchosporium* on barley, *Venturia* on apples and decreases the growth rate of *Ustilago maydis*. [3.325] It is recommended against rusts and mildews on cereals, coffee, grapes, apples and squash.

The main antifungal activity of paclobutrazole **3.36B** [76738-62-0] rests in the (+)-2*R*,3*R*-enantiomer. [3.065, 3.325, 3.329, 3.330] The crystal structure has been elucidated. [3.326] ¹⁴C-labeled paclobutrazole has been prepared. [3.122] Enantiomers have been separated by chiral derivatization and gas chromatography. [3.328]

Computer graphic alignment of 2*R*,3*R*-paclobutrazole with the 14 α -demethylation enzyme has resulted in a better guide for improved antifungal structures. [3.065]

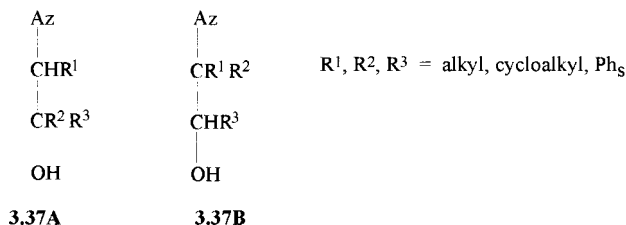
Though paclobutrazol inhibits *Botrytis cinerea*, *Sondaria fumicola*, *Fusarium graminearum*, *Sclerotium cepivorum*, *Bipolaris sorokiniana*, [3.331] and *Fusarium moniliforme*, [3.332] it has been developed as a systemic plant growth regulator (PGR), which constitutes the main activity of the (2*S*,3*S*)-enantiomer. [3.325, 3.329, 3.333] In general, 4-chloro derivatives like **3.36B** are less fungicidal and more plant growth-regulating than the 2,4-dichloro derivatives. PGR action here originates from inhibition of gibberellin biosynthesis. The agent is applied through injection into the trunk of maple, pine, oak and elm trees. [3.295]

3.2.3.2 α -(Aryl or aralkyl), β -(alkyl, aryl or aralkyl)-1-(2-hydroxyalkyl)-1H-azoles

These title compounds have been claimed as fungicides and display activity against *Erysiphe graminis* on barley, *Sphaerotheca fuliginea* on cucumber, *Pyricularia oryzae* on rice and *Uncinula necator* on grapevines. [3.334, 3.335, 3.336, 3.337, 3.338, 3.339, 3.340]

3.2.4 α,α,β - and α,β,β -trisubstituted, and $\alpha,\alpha,\beta,\beta$ -tetrasubstituted 1-(2-hydroxyalkyl)-1H-azoles

Title substances **3.37A** and **3.37B** have been claimed as fungicides with activity against *Erysiphe graminis* on wheat and barley, *Venturia inaequalis* on apple, *Cercosporidium personatum* on peanut and other plant pathogens. [3.316, 3.341, 3.342, 3.343, 3.344, 3.345, 3.346, 3.347, 3.348]

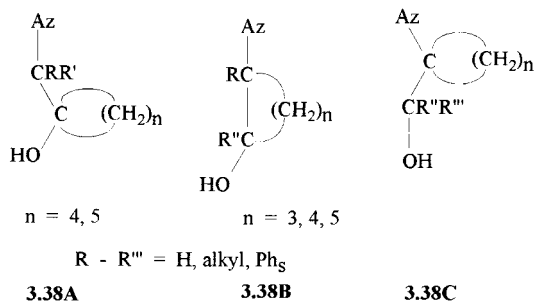


Synthesis with high diastereoselectivity can be achieved by Grignard addition to α -(1H-1,2,4-triazol-1-yl)ketones.[3.349] The products inhibit mildews and *Botrytis cinerea* on grapevine.

$\alpha, \alpha, \beta, \beta$ -Tetrasubstituted title compounds include some in which the β -C is part of a cyclopropane ring.[3.350, 3.351] Compared with ketoconazole, superior oral efficacy has been seen against experimental candidiasis.

3.2.5 1-(2-Hydroxyalkyl)-1H-azoles with α - and/or β -carbon as part of a cycloalkane

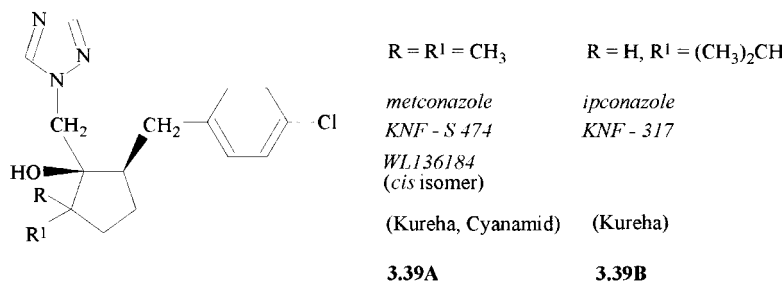
All three possible products **3.38A**, **3.38B** and **3.38C** have been described.



A large number of claims for 1-azolylmethyl-2-benzylcyclopentanol **3.38A** ($\text{R} = \text{R}^1 = \text{H}$, $n = 4$) have been applied as inhibitors of *Erysiphe graminis tritici*, *Puccinia recondita* and *P. striiformis* on apple seedlings, *Cochlibolus miyabeanus*, *Giberella fujikuroi* and *Pseudomonas glumae* and other pathogens on rice, and *Pyricularia oryzae*. [3.352, 3.353, 3.354, 3.355, 3.356, 3.357, 3.358, 3.359, 3.360, 3.361, 3.362, 3.363, 3.364, 3.365, 3.366, 3.367, 3.368, 3.369, 3.370, 3.371, 3.372, 3.373] In one patent application the benzyl group is replaced by a cyclohexylmethyl substituent.[3.374]

Some of these products have been recommended as preservatives for flowers.[3.375, 3.376, 3.377] Other examples from these series control wood-attacking fungi such as *Gleophyllum trabeum*, *Coniophora puteana*, *Poria placenta*, *Lentius tirinus*, *Coriolus versicolor* and *Streureum* spp.[3.367, 3.368]

From this large body of compounds, metconazole and ipconazole have been developed.[3.378]



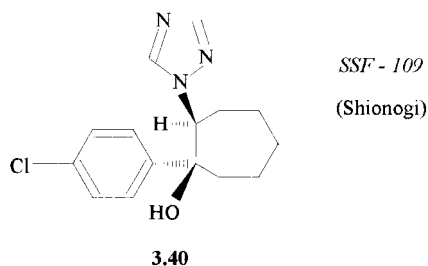
Metconazole **3.39A**, [125116-23-6] with the hydroxy and the benzyl group in *cis* position and (1*RS*,5*RS*; 1*RS*,5*SR*) conformation in the active ingredient, combats diseases in cereals caused by *Septoria tritici*, *S. nodorum*, *Puccinia* sp., *Erysiphe* sp., *Fusarium* sp., *Rhynosporium secalis*, *Pyrenophora teres*; in betterae: *Erysiphe b.*, *Uromyces b.*, *Cercospora b.*, *Ramularia b.*; on rape seed and sun flower: *Alteria brassica*, *Sclerotinia sclerotiorum*; on grape: *Uncinula necator*, *Guignardia bidwellii*. [3.379, 3.380, 3.381] Formulations with Dobanol increase foliar activity. [3.382]

Ipconazole **3.39B** [125225-28-7] has been recommended for treatment of rice seeds. [3.383, 3.384] Its metabolism has been investigated. [3.385]

A smaller set of claims have been filed for azolylcyclohexanols, -heptanols up to -decanols, and include azolylmethyl-dibenzocyclohepten-5-ol. [3.386, 3.387, 3.388, 3.389, 3.390] Activity against *Puccinia recondita* and *Erysiphe graminis* on wheat, *Botrytis cinerea* on beans, and *Pyrenophora teres* has been observed.

Title substances of the general formula **3.38B** incorporate cyclohexanols, cycloheptanols, and benzocyclohexanols. [3.391, 3.392, 3.393] They have been claimed as antimycotics and fungicides, with *in vivo* activities against *C. albicans* and *Trichophyton mentagrophytes*. The activities of a series of substances **3.38B** against *Botrytis cinerea* have been determined and evaluated using Hansch regression analysis and computer graphics. [3.394] Activity increases with molecular hypophobicity and with ring size, and decreases with *m*-substitution of the aryl substituent.

From these, agent SSF-109, **3.40** [129586-32-9] has been studied in more detail. [3.395]



The *cis*-isomer is 10–70 times more active than the *trans* form against *Phytophthora melonis* and a number of Ascomycetes, Basidiomycetes, and Fungi imperfecti. [3.396] Only against *Rossellinia necatrix* the *trans* isomer is 14 times more

active than the cis form. *In vivo*, SSF-109 controls infection of cucumber by *B. cinerea*, *S. fulginea* and *S. sclerotiorum*, rice against *P. oryzae* and *R. solani*, wheat against *E. graminis* and oat against *Puccinia coronata*.

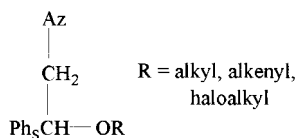
The enantiomers of SSF-109 have been separated. (–)-SSF-109 is five times more active against *B. cinerea* and two to four times more active against powdery mildew and grey mold than the (+)-isomer. A similar relationship holds for plant growth retardant activity in this series.[3.396, 3.397]

Apparently, only one example of ring structure **3.38C** has been claimed in the form of 1,1-disubstituted cyclopropane derivatives ($n = 2$, $R'' = R''' = \text{Ph}_s$) with p.o. activity against *Candida albicans* infection of mice.[3.398]

3.3 Ethers of 2-hydroxyalkyl-1H-azoles

3.3.1 α -Substituted 1-(2-alkoxyalkyl and 2-alkenoxyalkyl)-1H-azoles

A number of title compounds **3.41** with one α -substituent have been claimed as fungicides and agrochemical microbicides.[3.399, 3.400, 3.401, 3.402, 3.403, 3.404, 3.405, 3.406, 3.407, 3.408, 3.409, 3.410].



3.41

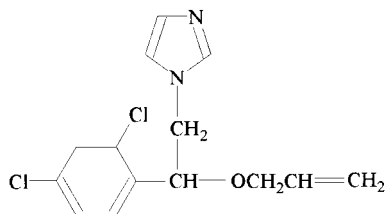
A smaller group of claims covers compounds with two or three substituents at α - and/or β -positions. [3.411, 3.412, 3.413] Substances of these series inhibit *Trichophyton* sp. or *Candida albicans* infection in mice, *Erysiphe graminis* and *Puccinia graminis* on wheat and *Drechsleriana graminea* on barley.

From these groups of compounds, Enilconazole has been developed in the early seventies, and tetraconazole and a geranyl ether more recently.

Enilconazole **3.42A**, [35554-44-0] is marketed under this name as a veterinary antimycotic.[3.093, 3.414]

The drug is applied from smoke pellets in poultry houses with chickens infected by *Aspergillus fumigatus*, which attacks these animals in their first days of life. Imazalil drug lowers the death rate by a factor of 3.7 compared with placebo.[3.415] As a disinfection agent in rabbit farms, the drug reduces *Microsporum canis* infection with a factor of 35 compared with placebo.[3.416]

For agricultural marketing, the same compound has been named imazalil **3.42B** [35554-44-0].[3.417, 3.418] It can be adsorbed on bentonite, which might be useful



enilconazole

veterinary

(Janssen)

3.42A

imazalil

agro

R-23,797 (base)*R*-27,180 (sulfate)

(Janssen)

3.42B

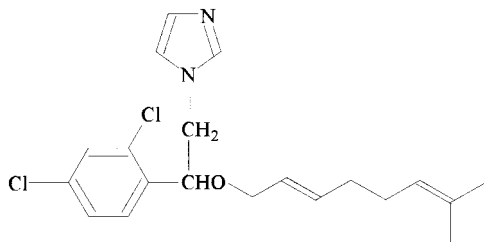
for application.[3.419] Emusifiable concentrations have been claimed.[3.420] The drug has also been recommended as a component for washing and cleaning mixtures.[3.421]

Imazalil inhibits *Diplodia natalensis* and *Alternaria citri* *in vitro*.[3.425] It reduces infection of *Drechsleriana graminea* on barley.[3.426] Incorporated into packing film, it prevents development of *Penicillium digitatum* on oranges.[3.425] The antisporulant activity of imazalil recommend it for post-harvest treatment of apple and citrus fruit.[3.427] Dipping lemons in aqueous imazalil solution at 50°C greatly reduces the doses for control of post-harvest decay.[3.425, 3.429] Emulsions of the agent control *Erysiphe cichoracearum*.[3.430]

A recent survey covers imazalil residues on citrus fruits.[3.422, 3.427] The fate after treatment of apples, during storage and on juice production has been followed.[3.423, 3.427] A two-phase titration method seems to be useful on-site.[3.431]

For field use it can be important that imazalil is taken up by earthworms.[3.424]

Tolerances for imazalil and its metabolites have been set on raw agricultural commodities. [3.432, 3.433, 3.434]



AFK - 108

(Kao)

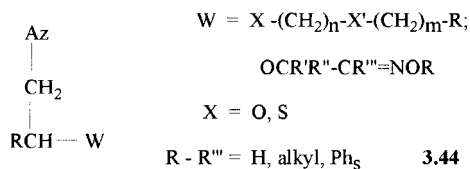
3.43

The geranyl ether AFK-108, **3.43** [135330-85-7] has been designed for simultaneous action at the site of the heme iron and at the substrate binding site of lanosterol 14 α -demethylase from *S. cerevisiae*.[3.399, 3.402, 3.408, 3.435]

As expected, the geranyl group as hydrophobic substituent acts through its similarity with the sterol side chain. Enzyme inhibition is indeed at an optimum, compared with similar derivatives with the longer farnesyl or the shorter prenyl groups replacing geranyl. The order of P-450 inhibition correlates with spectrophotometrical activity. Possibly the 2,4-phenyl group of AFK-108 recognizes the body of the sterol ring.[3.435]

3.3.1.1 α -Substituted [2-functionally substituted alkoxy)]-1H-azoles

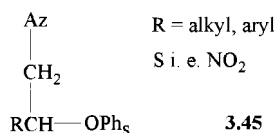
Title ether series **3.44** are derived from the previous title substances **3.41** by further functional substitution of the alkoxy groups.[3.436, 3.437, 3.438]



Some of these examples are active inhibitors of *Staphylococcus aureus*, *Candida albicans* and control *Erysiphe graminis* on barley.

3.3.2 1-(2-Aryl- or heterocycl-yl-oxy)alkyl-1H-azoles

A few series of title compounds **3.45** have been claimed as antifungals.[3.439, 3.440, 3.441, 3.442]

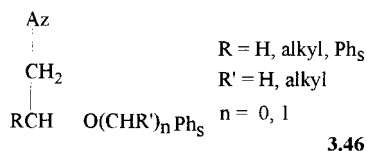


Some prevent infection of cucumber by *Sphaerotheca fuliginea*. [3.440] Another series with Ph_s = dibenzofuran-3-yl, as imidazolium salt, protects sweet peppers against *Botrytis cinerea*. [3.441]

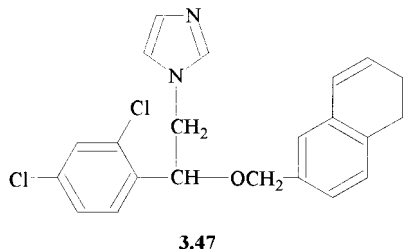
3.3.3 1-[2-(Halogenophenyl)]methyloxy)alkyl-1H-imidazoles; the econazole/miconazole family

3.3.3.1 General aspects

One series **3.46** of the title substances represent, when $\text{R} = \text{H}$, some of the rare straight (2-substituted phenylmethyloxy)ethyl azoles, which inhibit *Pyricularia oryzae* on rice.[3.443]

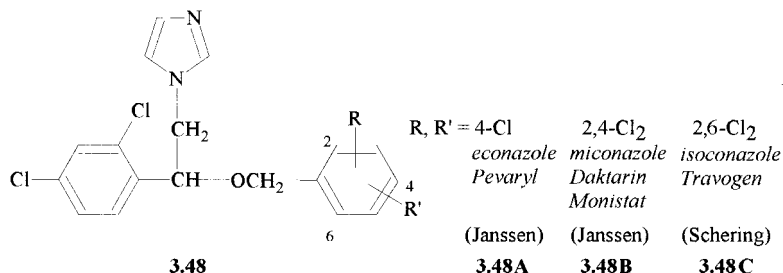


This series, but with $R = Ph_s'$, $R' = H$ and $n = 1$ has been reinvestigated extending to alkoxyphenyl, benzofuryl, and naphthyl in place of the two 2,4-dichlorophenyls of miconazole. Some of the products, e.g. **3.47** have outstanding *in vitro* activity against *C. glabrata* and *C. parapsilosis*. [3.444]



3.3.3.2 Econazole and miconazole: Chemical and pharmaceutical aspects

By far the most important title compounds are **3.48A**, econazole [base 27220-47-9; nitrate 24169-02-6] **3.48B**, miconazole [base 22916-47-8; nitrate 22832-87-7] and **3.48C**, isoconazole [57523-40-6], some of the first antimycotics in the late 1960s and still in wide use as both drugs and standards.

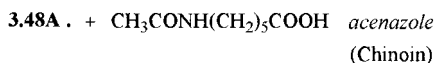


Synthetic improvements and new routes of preparation are still being published or claimed.[3.445, 3.446, 3.447, 3.448, 3.449, 3.450, 3.451, 3.452, 3.453, 3.454, 3.455, 3.456, 3.457]

Both enantiomers of each econazole and miconazole have been isolated using tartaric acids as resolving agents, or prepared from chiral imidazolylethanol derivatives, or by enantioselective reduction of the ketone intermediates with chiral oxazaborolidine.[3.458, 3.459, 3.460] The absolute stereochemistry has been derived from the crystal structure of (*R*)-(-)-econazole.[3.461, 3.461] The main *in vitro* activity of both drugs against *C. albicans*, *T. rubrum*, *T. gypseum*, *M. lanosum* and *A. flavus* rests in their (*R*)-(-)-enantiomers.[3.460] But (+)-econazole is racemized in rats after i.p. doses with $t_{1/2} = 1.24$ hours, which suggests that pure enantiomers of antifungal azoles may not always lead to a practical advantage in treatment.[3.463]

(Compare however the higher enantiomeric stability in the case of deschloro beclonazole, section 2.11.1).

The low solubility of miconazole has presented problems, especially for systemic application, and is reflected by the great amount of work concerning the physical and physicochemical properties of these two drugs and their salts. Thus, X-ray powder diffraction studies have been carried out on the racemates.[3.461, 3.462] New salts, complexes and addition compounds have been reported, e.g. econazole with acexamidic acid to give **3.49**, acenazole [109351-15-7],[3.464] or for both econazole and miconazole with β -cyclodextrin. [3.252, 3.465]



3.49

The 5-sulfosalicylates of econazole and miconazole show improved activity against vulvovaginal candidiasis, *Trichomonas vaginalis*, and Gram-negative bacteria compared with the usual nitrates, which is explained by their higher lipophilic character.[3.466, 3.467, 3.468, 3.469, 3.470]

Chemical stability of econazole and miconazole nitrates has been determined in the presence of benzoyl peroxide,[3.471] of miconazole base in vegetable oils,[3.472] in peritoneal fluid, [3.473] and as complexes of heavy metals.[3.474] Autoxidation products of econazole and miconazole have been characterized.[3.475]

A large number of formulations have been claimed for both drugs to overcome the low solubility. [3.476, 3.477, 3.478, 3.479, 3.480, 3.481, 3.482, 3.483, 3.484, 3.485, 3.486, 3.487, 3.488, 3.489, 3.490, 3.491, 3.492, 3.493, 3.494, 3.495, 3.496] The pharmacokinetics of formulations has been compared using solid-phase extraction of plasma followed by HPLC.[3.497, 3.498]

Cations as well as pH affect the action of miconazole on yeast plasma membranes.[3.499, 3.500, 3.501] Lethal action of miconazole on *C. albicans* is optimal at pH 6.0 to 7.0, at the lowest solubility of the drug, which may be caused by a solution of extremely small aggregates.[3.502]

Computer Assisted Molecular Design (CAMD) allows a three-dimensional model of the cytochrome-P450/miconazole complex to be plotted.[3.503]

3.3.3.3 Econazole and miconazole: Preclinical and clinical aspects

The usefulness of miconazole has been critically reviewed.[3.504] It is still generally used against dermatophytic infections of the skin, tinea versicolor, cutaneous and vaginal candidiasis. [3.505] There is scattered evidence of its activity against *Propionibact. acnes*,[3.506, 3.507] subconjunctival candidal keratitis,[3.508, 3.509] palatal and oral candidiasis,[3.510, 3.511] *Neisseria gonorrhoeae*,[3.512] and its use as an antiperspirant.[3.513] Of rarer microbial pathogens, miconazole inhibits *Candida endophthalmitis*,[3.514] *Helicobacter pylori*,[3.515] *Malassezia furfur*,[3.516] *Mucor ramosissimus*, [3.517] *Plasmodium falciparum*, [3.518] *Rhizoctonia* sp., *Paecilomyces lilacinus* and *Fusarium solani*. [3.519]

Contact dermatitis has been seen after p.o. treatment with miconazole.[3.520] The agent has shown outstanding therapeutic results in Japan, i. e. in clearing cryptococcal meningitis in 50%, and aspergillosis in 75% of the cases. These are

not comparable with results in Western countries. [3.521] The drug is the therapy of choice against infection by *Pseudoallescheria boydii*. [3.522]

Miconazole has been used to produce a mutant of *Rhodotorula glutinis* which improves the production of β -carotene by this Basidiomycota. [3.523]

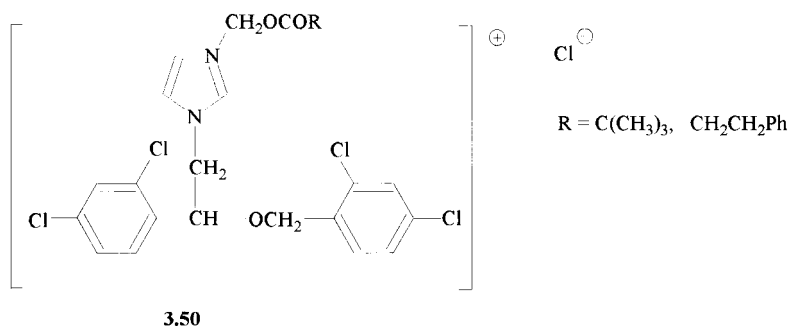
Econazole **3.48A** is recommended for topical treatment of dermatophytic skin infections, tinea versicolor and cutaneous candidiasis. [3.524]

3.3.3.4 Isoconazole and other close relatives

Isoconazole **3.48C** [base 27523-40-6; nitrate 24168-95-5] as base in an ethanol—propylene glycol medium, displays about 10-fold antimycotic activity in the living epidermis and dermis compared with that of other galenic preparations. [3.525, 3.526] The drug has been successfully tried for the treatment of human vaginal mycoses. [3.527, 3.528] It has been recommended for non-irritating fungicidal eye drops. [3.529]

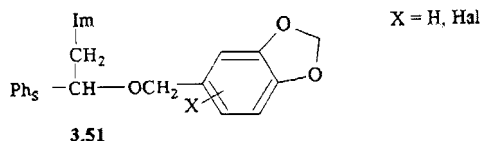
The fluoro analog ($R = H$, $R' = 4F$) of econazole **3.48A**, shows 10–14 times higher antimicrobial activity than econazole. [3.530]

Imidazolium compounds **3.50** have been claimed as fungicides and bactericides. [3.531, 3.532]



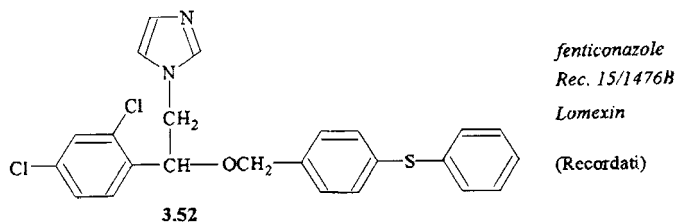
3.3.3.5 Further 1-(2-subst. phenylmethyloxy)-alkyl-1H-azoles related to miconazole

Bactericidal and fungicidal piperonylethers **3.51** have been claimed. [3.533]



Fenticonazole **3.52** [72479-26-6] is endowed with higher activity than clotrimazole and miconazole against Gram-positive bacteria which often superinfect skin diseases caused by fungi. [3.534]

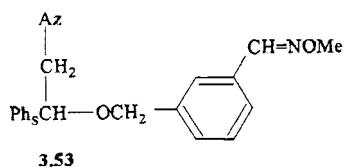
It shows excellent fungistatic activity against a wide range of dermatophytes, filamentous fungi and yeasts and is also fungicidal on dermatophytes. In the treat-



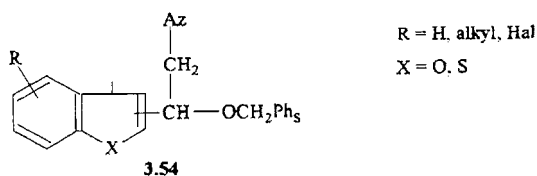
ment of vaginal candidiasis, the action of fenticonazole sets on more rapidly than that of miconazole.[3.534]

The improvement of dissolution has been investigated.[3.535, 3.536]

Triazole analogs of miconazole such as **3.53** show superior activity against *Leptospaeria nodorum* on wheat.[3.537]

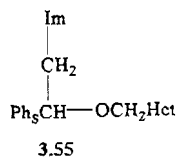


A series of bicyclo-heterocyclic analogs **3.54** has been claimed as fungicides.[3.538, 3.539]



3.3.3.6 1-(2-Heterocyclalkoxy)alkyl-1H-azoles

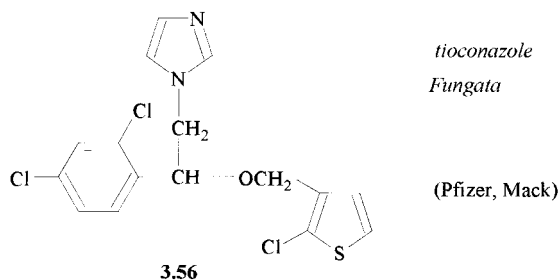
A number of title compounds **3.55** have been investigated.



As heterocycles, tetrazoles,[3.540] furanes and pyridines have been used, but thiophen proved to be most successful.[3.541, 3.542, 3.543] From these, tioconazole **3.56**, [65899-73-2] has been developed. [3.255, 3.544, 3.545, 3.546]

The racemate can be separated by chiral HPLC, optimized by a mathematical model.[3.547]

The fungicidal activity to that of tioconazole is at least equal to that of clotrimazole and miconazole, and is little affected by pH or serum.[3.546, 3.548, 3.549]



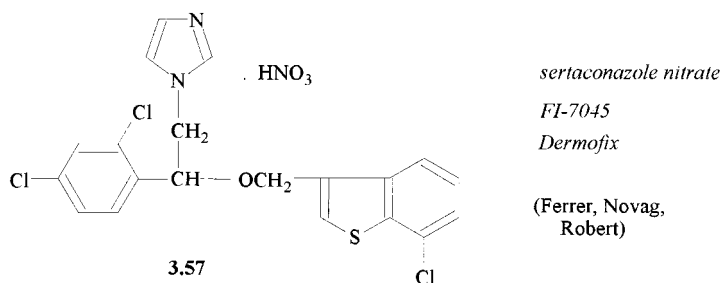
tioconazole
Fungata

(Pfizer, Mack)

The drug is very well tolerated and used for superficial mycosis of the skin and vaginal candidiasis.[3.545, 3.550] A solution in undecylenic acid has been recommended for the treatment of nails.[3.551, 3.552] Special preparations have been proposed against herpetic infections.[3.553]

Tioconazole is known however as a contact allergen.[3.554]

Title compounds **3.55** with bicyclic heterocycles include benzofuran-3-yl,[3.555] and benzothiophen-2- and -3-yl-derivatives.[3.556, 3.557] From these, sertaconazole **3.57**, [99592-32-2] has been developed.[3.558, 3.559, 3.560]



sertaconazole nitrate

FI-7045

Dermofix

(Ferrer, Novag,
Robert)

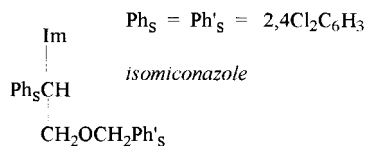
Naphthalene-1,5-disulfonates have been investigated besides the usual nitrate.[3.558]

Sertaconazoles antimicrobial activity equals or surpasses that of miconazole, tioconazole and bifonazole.[3.561, 3.562, 3.563] It has been recommended for the treatment of cutaneous dermatoses and vaginal candidiasis.[3.560] With two applications daily, the usual topical treatment is 4 weeks.[3.559]

3.3.4 β -Aryl-1(2-hydroxyethyl)-1H-azole ethers

Title compounds **3.58** have been prepared following the idea of an iso-miconazole ($\text{Ph}_s = \text{Ph}_s' = \text{C}_6\text{H}_3-2,4\text{Cl}_2$).[3.564]

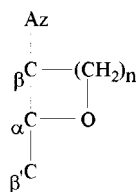
Some of these compounds show less cytotoxicity than miconazole, but their inhibition of pathogenic fungi is inferior to that of miconazole or bifonazole. However, iso-miconazoles potency against *Staph. aureus* is close to that of streptomycin.[3.564]



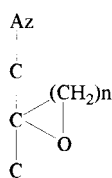
3.58

3.3.5 Cyclic analogs of 1(2-hydroxyalkyl)-alkyl-1H-azole ethers

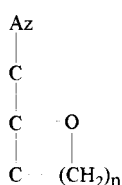
Cyclization of the α oxygen to α , β or β' C-positions will form general structures **3.59A**, **3.59B** and **3.59C**



3.59A



3.59B



3.59C

For $n = 0$, classes **3.59A** and **3.59C** represent oxirans (epoxides), which will be discussed in section 3.13. This is also true for $n = 1$ in class **3.59B**.

For $n = 1$, classes **3.59A** and **3.59C** represent oxetans, as does $n = 2$ in class **3.59B**. These structures will be discussed in section 3.16.

For $n = 2$, classes **3.59A** and **3.59C** represent tetrahydrofurans, as does $n = 3$ in class **3.59B**. These have been discussed under azol-1-yl-heterocycles in section 2.3 and under azol-1-ylmethyl-heterocycles in section 6.1.

By similar manipulations with $n > 3$, tetrahydropyrans result which are also discussed in section 6.1.

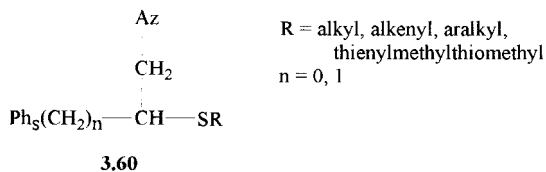
3.4 Thioanalogs of the econazole/miconazole family

3.4.1 1-(1-(2-Alkylthio)alkyl)-1H-azoles

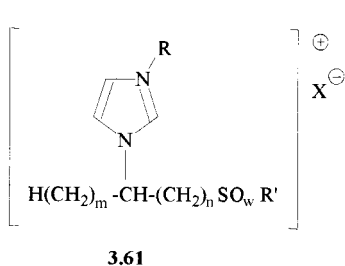
Replacing oxygen by sulfur in the econazole/miconazole family was started early in the history of azole antimycotics [1.01] and has been continued ever since, to arrive at compounds of the general structure **3.60**. [3.565, 3.566, 3.567]

Such a substance with $\text{Az} = \text{Im}$, $\text{R} = \text{Bu}$, $n = 0$ and $\text{S} = 2,4\text{-Cl}_2$ controls powdery mildew on bean plants. [3.565]

Related alkylthio(polyethylimidazolium) derivatives **3.61** have been claimed as biocides and bactericides. [3.568]



R = alkyl, alkenyl, aralkyl,
thienylmethylthiomethyl
n = 0, 1



A : m = 0, n = 1

B : m = 1, n = 0

p = 2 - 15

R = alkyl, PhCH₂, HOCH₂CH₂

R' = 12 - 18C alkyl

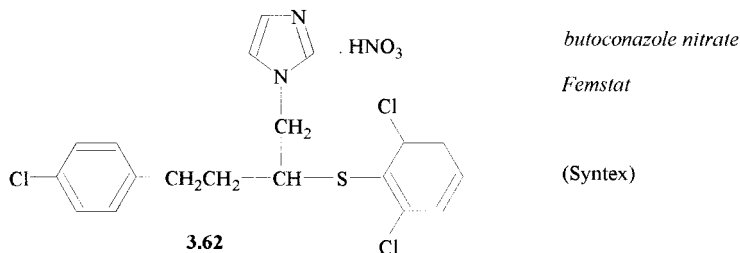
w = 0, 1, 2

X = inorganic or organic anion

3.4.2 1-(2-Aryl- or heterocyclyl-thio)alkyl-1H-azoles

In title compounds of the general structure **3.60**, R has been replaced by phenyl or pyridyl.[3.569, 3.570, 3.571, 3.572, 3.573] They inhibit e.g. *Puccinia recondita* on wheat, *Venturia inaequalis*, *Erysiphe cichoracearum* on cucumber seedlings, and *Podosphaera leucotricha* on apples.

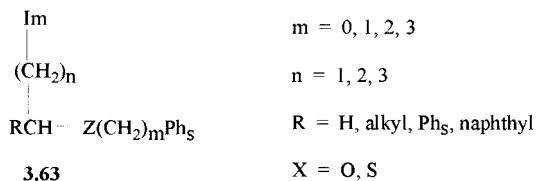
From these, butoconazole **3.62**, [64272-76-0] has been selected for the treatment of vaginal candidiasis.[3.574, 3.575, 3.576, 3.577]



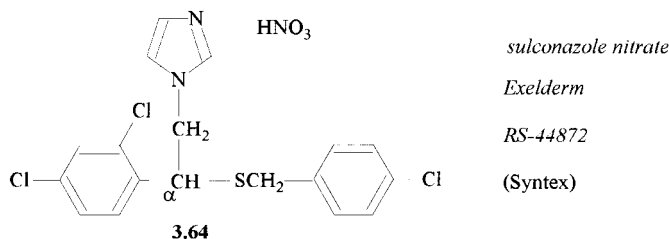
Pure (S)- and (R)-enantiomers have been prepared from the respective chiral glycidyl tosylates.[3.578] They show similar inhibitory activity against *C. albicans*.

3.4.3 1-(2-Benzylthio)alkyl-1H-azoles

These title substances **3.63** include the thio analogs closest to the econazole/miconazole family.[3.579, 3.580, 3.581]



From these, sulconazole **3.64** [61318-90-9] has been developed,[3.582, 3.583, 3.584] and stabilized. [3.585, 3.586]

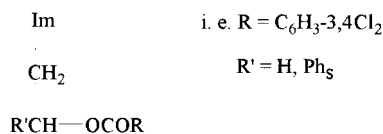


The drug was also prepared with a ^{14}C -label on the α -C.[3.587]

The antifungal effect of sulconazole is similar to that of clotrimazole with an activity against *Cryptococcus neoformans* much higher compared with the standard. [3.588] Its percutaneous absorption in humans is higher than that of clotrimazole and miconazole. [3.589]. It is of similar efficacy as miconazole in curing experimental *Trichophyton mentagrophytes* infection in guinea pigs.[3.590, 3.591] After large overdosing, the drug produces embryotoxic effects in rats.[3.583]

3.5 Esters and carbamates of 1-(2-hydroxyalkyl)-1H-azoles

Esters **3.65** which cause little irritation to the skin have been recommended against acne and seborrhoea.[3.592]



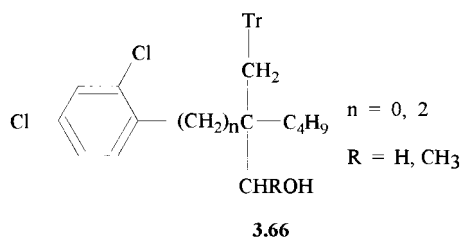
Another series of compounds **3.65**, with $\text{R}' = \text{-C}_6\text{H}_3\text{-2,4Cl}_2$ and $\text{R} = \text{C}_1$ to C_{11} alkyl, presents its maximum inhibition of *Candida* sp. with $\text{R} = \text{Bu}$.[3.593]

Similar triazol derivatives were described as fungicides, inhibiting *Puccinia recondita* on wheat.[3.594, 3.595] Esters with permethric acid protect cucumber against *Sphaerotheca fuliginea*,[3.596] and barley against *Erysiphe graminis*. [3.597]

3.6 1-(3-Hydroxyalkyl)-1H-azoles, their thio analogs, homologs and derivatives

3.6.1 1-(3-Hydroxyalkyl)-1H-azoles and their ethers

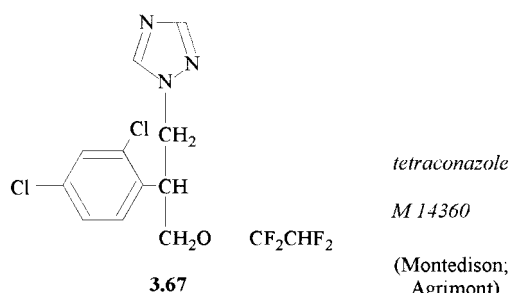
Fungicidal title compounds like **3.66** ($n = 0$, $R = H$) have been claimed as agricultural fungicides. [3.598]



A related substance, with $n = 2$, $R = CH_3$ in the form of the 1,2,4-triazole oxide, displays fungicidal and plant growth-regulating activity.[3.599]

Some 1-(3-subst. phenoxypropyl)-1H-pyrazoles have been claimed as pesticides for the control of *Aphis gossypii* larvae on cucumber seedlings.[3.600]

Ethers of the title compounds **3.66** display good activity against *Candida albicans*. [3.601] From this series, tetraconazole **3.67** [112281-77-3] has been developed as a foliar fungicide.[3.418, 3.602, 3.603]

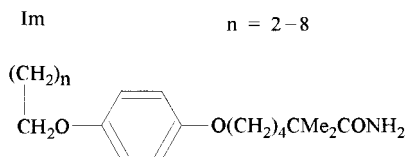


The agent is recommended for use against *E. graminis*, *Puccinia* spp., *Septoria*, *Rhynchosporium secalis* on cereals, against *P. leucotricha* on apples, against *C. beticola*, *Uromyces*, *Erysiphe* and *Rumularia betae* on sugar beet, against *U. necator* on grapes, and rusts and mildew diseases of peach and ornamental plants.

Both enantiomers of tetraconazole have been prepared.[3.604, 3.605] Highest activity again rests within the (R)-(+)-enantiomer against *Botrytis cinerea*, *Cercospora beticola*, *Guignardia bidwellii*, *Pyricularia oryzae*, *Sclerotinia minor*, *Sclerotium cepivorum* and *Cladosporium cucumerinum*. The more active (R)-(+)-enantiomer achieves *in vitro* activity ratios R/S from 1.9g against *P. oryzae* and *P. oryzae* up to 19.6 against *Botrytis cinerea*, and reaches a dramatic value of 400 against *E. graminis* on wheat.[3.604, 3.605]

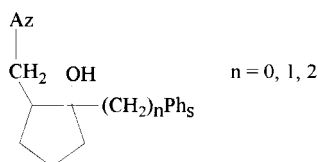
3.6.2 Homologs and cyclic analogs of 1-(3-hydroxyalkyl)-1H-azoles

Some homologs **3.68** of the preceding series reduce Ehrlich tumor cells in mice;[3.606] others inhibit picornavirus in HeLa cells.[3.607]



3.68

Cyclic analog **3.69** with $n = 0$ inhibits *Puccinia recondita* on wheat and has been claimed as a fungicide.[3.608]



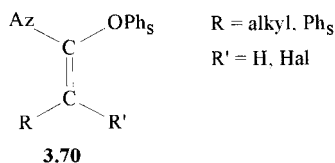
3.69

Carbinolethers similar to **3.69**, in which C_α and C_β are part of a bicyclic heterocycle, such as 2,3-dihydrobenzo[b]thiophene, have been discussed earlier (see section 2.5.1, ciskonazole).

3.7 1-(x-Hydroxy-1-alkenyl)-1H-azoles

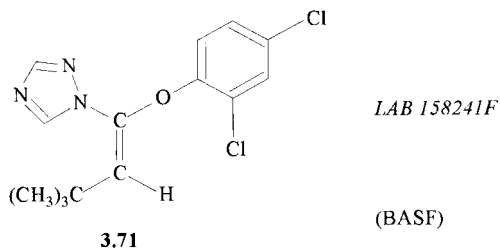
3.7.1 1-(1-Hydroxy-alken-1-yl)-1H-azoles, their ethers and homologs

Title compounds **3.70**, also called ketene N,O-acetals, have been claimed as fungicides.[3.609, 3.610, 3.611, 3.612, 3.613, 3.614]



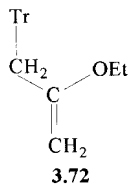
They can be prepared by elimination of toluenesulfonic acid from 1-phenoxy-2-hydroxy-allyl)-1H-azole tosylates with sodium sulfide or Me_3COK . These compounds protect wheat against *Erysiphe graminis*, cucumber against *Erysiphe cichoracearum* and tomato against *Phytophthora infestans*. They were also recommended for the protection of wood against fungal attack.

From these series, substance **3.71**, LAB 158241F [95059-87-3] has been selected for further studies as a fungicide.

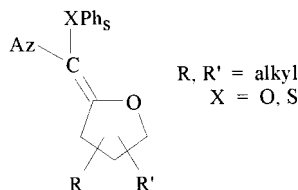


It causes accumulation of 14α -methyl sterols at the expense of Δ^5 -sterols by inhibition of P-450^{OBT.14DM} from maize embryos.[3.615]

Homologs **3.72** of the title compounds can be prepared from reaction of 1,2,4-triazole with propargylbromide, followed by ethanol addition. [3.616]

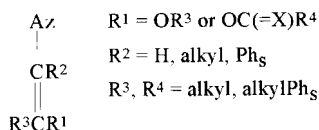


Cyclic analogs **3.73** of the title compounds have been claimed as antimycotics and fungicides with activity against *Trichophyton mentagrophytes*, *Sphaeroteca fuliginea* on cucumber, *Piriculatia oryzae* on rice and *Leptosphaeria nodorum* on wheat.[3.617, 3.618, 3.619, 3.620]

**3.73**

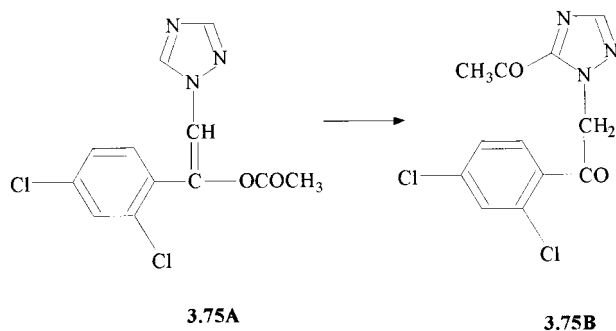
3.7.2 1-[2-(Alkoxy- or alkylthio)-ethenyl]-1H-azoles

Title compounds **3.74** which can also be regarded as β -azolyl enol ethers or as 1-(1,2-disubstituted vinyl)-1H-azoles, have been claimed as fungicides.[3.621, 3.622, 3.623, 3.624]

**3.74**

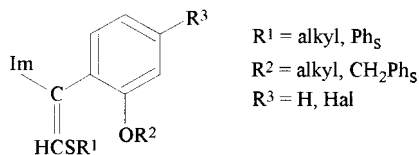
These compounds inhibit *Bacillus subtilis*, *Puccinia graminis* on wheat, *Cercospora arachidicola* on peanut, *Erysiphe graminis* on barley, *Venturia inaequalis* on pom buds, *Erysiphe cichoracearum* on cucumber seedlings and *Botrytis cinerea* on beans.

Further, enol acetates **3.74** (R¹ = OCOR⁴, R² = alkyl, R³ = Ph_s, R⁴ = alkyl, Ph_s) have been claimed as fungicides.[3.621, 3.625] In acetic anhydride, the acyl group of **3.75A** rearranges into a diketone **3.75B** in good yield.[3.626, 3.627, 3.628]



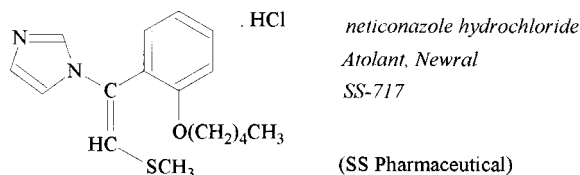
(Enol phenacylethers with fungicidal activity appear as isomers in the synthesis of 2-(1H-triazol-1-yl)alkane-1,4-diketones; see section 4.3).

Thio analogs of **3.76** are promising inhibitors of dermatophytes and yeasts.[3.629]

**3.76**

The optimum total of carbon atoms of alkyls R^1 and R^2 is 6 to 7. X-ray data have been supplied. (Z)-stereomers are slightly less active than (E)-forms.

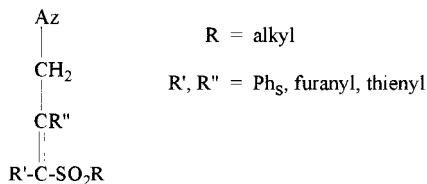
From these, neticonazole **3.77** [130773-02-3, base 130726-68-0] has been developed.[3.630, 3.631, 3.632]

**3.77**

In vitro activity with or without serum against a number of pathogenic fungi is considerably higher than that of clotrimazole or miconazole and similar to that of bifonazole.[3.633] It is especially active against *Candida glabrata*, *Trichophyton*, *Microsporum*, *Aspergillus* and *Fonsecaea* spp.[3.623, 3.630] Clinical experience demonstrated neticonazole as a safe and effective treatment of mycoses like trichophytosis, candidiasis, and different types of tinea.[3.631] Topical formulations with reduced skin irritation have been claimed.[3.634]

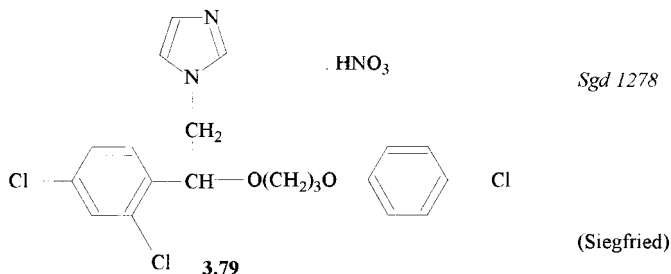
A homolog to **3.77**, with hexyloxy replacing pentyloxy, has similar *in vitro* activities also closely resembling bifonazole.[3.629]

A series of other homologs **3.78** in which the thio group is oxidized, control *Echinochloa crus-galli* and *Erysiphe graminis*.[3.635]

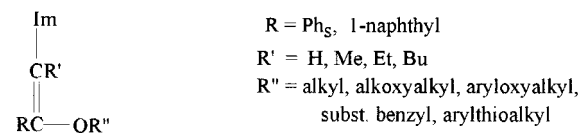
**3.78**

3.7.3 1-(2-Aryloxy-alkyloxy)-(1-alkenyl)-1H-azoles

Title compounds, which might also be regarded as 2-(1H-azol-1-yl)vinyl-ethers, have been discovered by first extending the $-\text{OCH}_2-$ substructure of econazole **3.48A** to $-\text{X}(\text{CH}_2)_n \text{X}'-$ with $\text{X}, \text{X}' = \text{O}, \text{S}$ and $n = 1$ to 4, hoping to increase solubility in water. The first series of products culminated in a substance **3.79** with higher i.v. antimycotic activity than the standard, much lower toxicity in mice, and better curative action in the treatment of vaginal candidiasis in rats.[3.636]

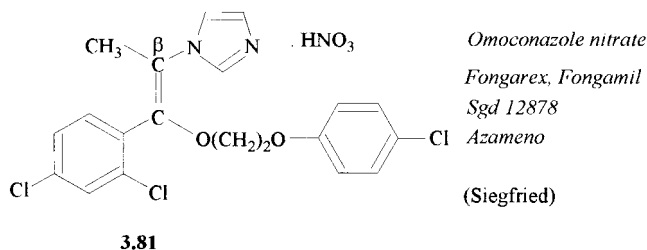


It has same potency as econazole in the curative treatment of *Trichophyton mentagrophytes* infection of the guinea pig. In search for further improvement, it was attempted to introduce a new substructure at the β -position of the 1-(1H-imidazol-1-yl)methyl aryl ketone intermediates to create at a new center of asymmetry. Surprisingly, enol ethers **3.80** with interesting antimycotic activities are formed as main products.[3.636]



3.80

Thus, the new antimycotic omoconazole **3.81** has evolved.[3.559, 3.636, 3.637, 3.638, 3.639]



Toxicity has been found in the order of econazole for $\text{R}'' = \text{alkoxyaalkyl}$, but is much lower for compounds with $\text{R}'' = \text{phenoxyalkyl}$.[3.636]

Synthesis has been improved by PTC to avoid chromatographic separation of the *E/Z*-product mixture.[3.637, 3.639] It is of interest, that the precursor 2-(4-chlorophenoxy)ethanol, mycotetracid [1892-43-9], has been used as disinfectant and antimycotic from the pre-azole period.[3.640]

The (*Z*)-stereostructure of omoconazole has been confirmed by NMR and X-ray analysis.[3.641] The corresponding (*E*)-isomer shows a much lower antimycotic potency and a much higher toxicity. The drug displays superior *in vitro* activity against *C. albicans*, *C. neoformans*, *Torulopsis candida*, *Trichophyton mentagrophytes* and *A. fumigatus* compared with that of democonazole (see below) and **3.79**. In its action against *A. fumigatus*, pronounced superiority to miconazole and ketoconazole has been demonstrated.[3.642] Omoconazole is more toxic to Gram-positive bacteria than clotrimazole, miconazole or tioconazole.[3.559]

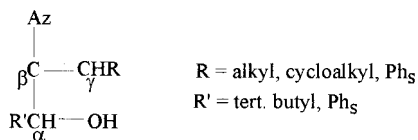
Antimycotic compositions with omoconazole have been designed,[3.643, 3.644, 3.645] and large-doses pharmacokinetics and safety have been determined.[3.646] The cream formulation shows high efficacy in the topical treatment of fungal infections of the skin, and the ovula in the local treatment of vaginal mycoses.[3.559, 3.647]

For democonazole [70161-09-0], the β -desmethyl analog of omoconazole, a GC assay method has been described.[3.648]

A number of other laboratories have claimed omoconazole analogs based on 1,2,4-triazole as fungicides.[3.649, 3.650, 3.651, 3.652, 3.653] Typical activities of these series are directed against *Erysiphe* spp. on wheat and barley, *Podosphaera leucotricha* and *Venturia inaequalis* on apple, *Cercospora beticola* on sugar beet, *Puccinia tritici* on wheat, *Pyricularia oryzae* on rice, *Cochliobolus sativus* and *Helminthosporium gramineum* on barley.

3.7.4 1- and 2-Azol-1-yl-1-propen-3-ols

Compounds **3.82** respresent the first group of the title compounds, which have also been named azole-1-ylvinylcarbinols or β -(azol-1-yl)substituted allylcohols.

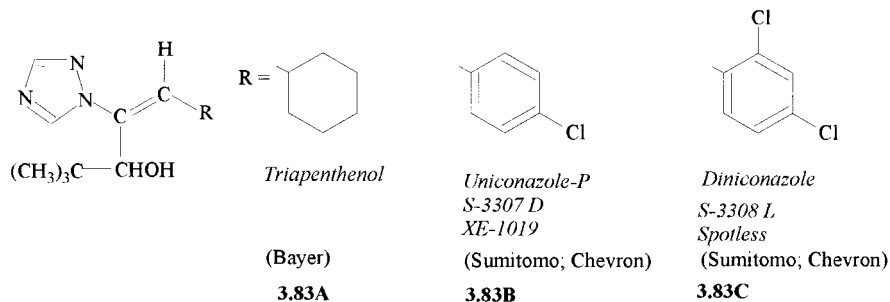


3.82

(The allyloxy group is also a structural fragment of enilconazole, see section 3.3.1). A large number of disclosures attest to the fungicidal and plant growth-regulator (PGA) activities of this series. [3.654, 3.655, 3.656, 3.657, 3.658, 3.659, 3.660, 3.661, 3.662, 3.663, 3.664, 3.665, 3.666, 3.667] The preferred stereoisomers have often been prepared by metal hydride reduction of the respective ketones.[3.668, 3.669, 3.670, 3.671, 3.672, 3.673, 3.674, 3.675, 3.676, 3.677]

From the above series, triapenthenol, uniconazole and diniconazole, all (*E*)-stereoisomers, have been developed.

Triapenthenol **3.83A**, [76608-88-3] is used as a plant growth regulator (PGR) in oilseed rape and in grasses grown for seed.[3.679]



Its PGR activity is centered in the (*S*)-(-)-enantiomer. In contrast, the (*R*)-(-)-enantiomer is mainly fungicidal. The resolution has been achieved via the (-)-menth-3-yloxyacetate which on hydrolysis with NaOH yields (+)-triapenthenol.[3.679, 3.680] This enantiomer can also be prepared by asymmetric reduction of the respective ketone.[3.681, 3.682] It protects barley from attack by *Cochlibolus sativus*. [3.679]

Uniconazole **3.83B**, [83657-22-1; (*E*)-isomer 76714-83-5]; has also been developed as uniconazole-P [(*E*)-(*S*)-(+)-isomer 83657-17-4; (*E*)-(*R*)-(-)-isomer 83657-16-3]. [3.683]

Uniconazole-P, endowed with the highest PGA, is recommended to increase flowering in ornamentals, trees and shrubs, and to reduce lodging in rice.[3.684] On acid treatment the (*Z*)-form isomerizes to the (*E*)-form.[3.685]

Diniconazole **3.83C**, [(*E*)-(\pm)-, 76714-88-0], is prepared as the (*E*)-(-)-enantiomer using a chiral borohydride reagent,[3.686] or by racemate separation.[3.686, 3.687] The product has been ¹⁴C-labeled in the triazole ring.[3.687] This substance reacts as a systemic and curative fungicide against powdery mildews and rusts on crop plants and on roses.[3.093, 3.689] Diniconazole controls *Puccinia arachidis* on peanuts and also shows PGA.[3.690] It also influences growth and monoterpene levels of garden sage and scotch spearmint.[3.691] The (-)-enantiomer is used as seed disinfectant e.g. against *Helminthosporium tramineum* on barley.[3.692]

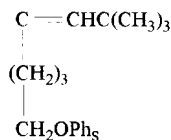
Diniconazole inhibits *Ustilago maydis* by interference with demethylation at C-14 of 24-methylendihydrolanosterol.[3.693]

A number of papers report the different fungicidal and PGR activity of the (*E*)- and the (*Z*)-stereoisomers of diniconazole.[3.694, 3.695, 3.696, 3.697, 3.698, 3.699]. The (*R*)-(-)-isomer shows the higher activity against *Ascomycotina*, *Basidiomycotina*, *Deuteromycotina* and *Gibberella fujikuroi* fungi, while the (*S*)-(-)-stereomer is strongest in plant growth inhibition, as demonstrated on cucumber seedlings.

Formulations of diniconazole have been claimed.[3.700, 3.701]

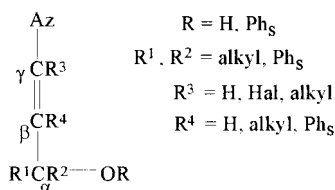
Compounds **3.84** represent homologs of **3.82**.

Az

**3.84**

They have been claimed as fungicides which control *Erysiphe cichoracearum* on cucumber.[3.702]

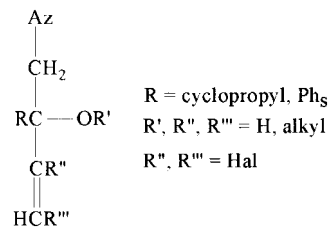
The second group of title compounds, γ -(azol-1-yl)substituted allyl alcohols **3.85** is represented by a few examples.[3.703, 3.704, 3.705, 3.706]

**3.85**

These compounds result from addition of Grignard reagents to 3-(imidazolyl)-2-alken-1-ones.[3.707] They inhibit *Piricularia oryzae* on rice, *Pyrenophora teres* on barley and *Botrytis cinerea* on beans.[3.706, 3.708]

3.7.5 α -(Azol-1-ylmethyl)-allyl alcohols and their derivatives

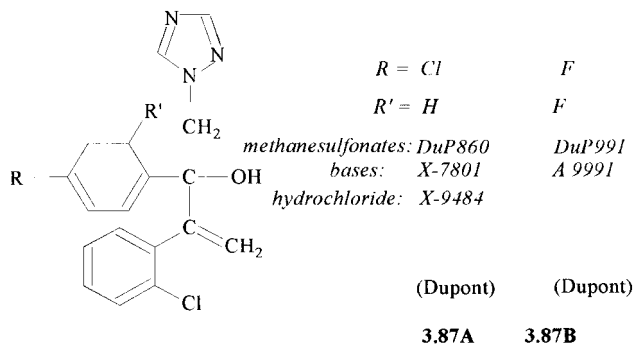
A large number of disclosures concern products of the general formula **3.86**.[3.710]

**3.86**

These have been claimed as medicinal and agricultural antifungals.[3.709, 3.710, 3.711, 3.712, 3.713, 3.714, 3.715, 3.716, 3.717, 3.718, 3.719, 3.720, 3.721, 3.722, 3.723, 3.726b] Some of these compounds show a high *in vivo* activity against *Candida albicans*, *Aspergillus niger* and *A. fumigatus* infections of

mice.[3.710, 3.711, 3.714] They also protect barley seedlings against e.g. *Pyrenophora teres*, *Erysiphe graminis*, *Cochliobolus sativus* and *Puccinia recondita*.

From these, DuP-860, **3.87A** [base, 124669-21-2] and **3.87B**, DuP 991 have been investigated as antimycotics.[3.724, 3.725]



The solubilities in water amount to 7.0 µg/mL for **3.87B** at pH 8.2 and 1.59 µg/mL for **3.87A** at pH 6.8. Co-solvents like proylene glycol, polyethylene glycol 400 or glycerol increase solubility but facilitate oxidative degradation.[3.725]

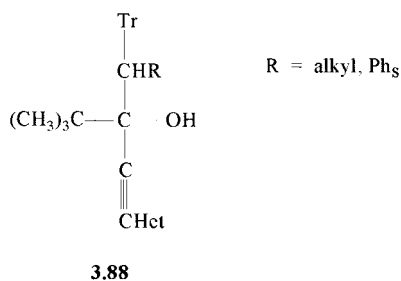
The hydrochloride of **3.87** is unstable at 60°C under liberation of HCl, but the base is stable under that condition, even on addition of water and irradiation.

When given p.o., both substances are active against *Aspergillus* and *Candida* infections in animals. DuP-860, in comparison with itraconazole and fluconazole, generally shows superior activity *in vitro* against *Candida albicans*, *C. tropicalis*, *C. parapsilosis*, *C. lusitaniae*, *C. guilliermondi*, *C. glabrata*, *Cryptococcus neoformans*, and *Aspergillus* spp. Pharmacokinetic characteristics include moderate $t_{1/2}$ values in experimental animals compared with those of fluconazole.[3.724]

DuP 860 has been discontinued from active development.[3.726]

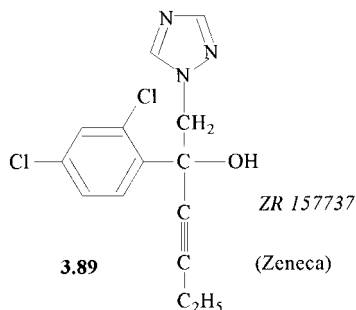
3.7.6 α -(Azol-1-ylmethyl)propargyl alcohols

Title compounds such as **3.88** have been claimed, sometimes including analog allyl structures, as fungicides.[3.709, 3.711, 3.716, 3.727, 3.728, 3.729, 3.730, 3.731, 3.732, 3.733, 3.734, 3.735, 3.736] Acetylenic intermediates have also been disclosed. [3.737]



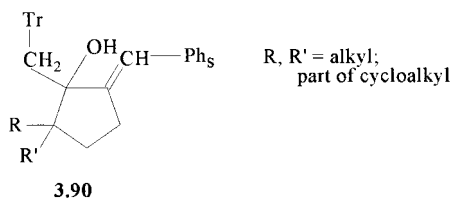
These compounds protect mice against *Candida* infection. They also show activity against *Puccinia recondita* on wheat and *Erysiphe graminis* on barley, but can also act as plant growth regulators.

One example **3.89**, ZR 157737 from these has been ^{14}C -labeled for detailed study as a potential fungicide.[3.122]



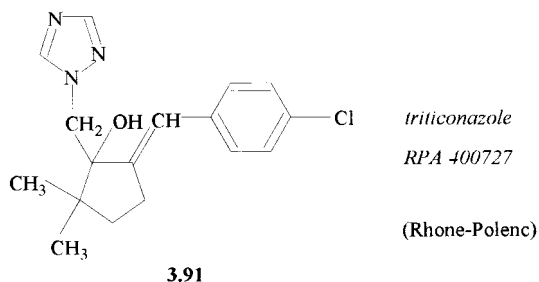
3.7.7 Cyclic analogs of azolyl-vinyl-carbinols

Series of cyclopentane compounds **3.90** with exocyclic C=C bond have been claimed as fungicides.[3.738, 3.739, 3.740, 3.741, 3.742, 3.743]



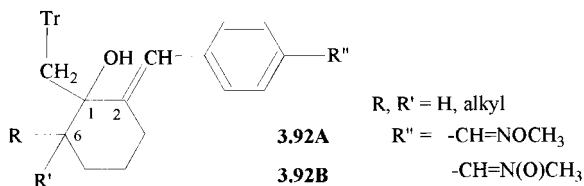
They protect tomato leaves against *Botrytis cinerea*, and inhibit *Penicillium brevicale*.

From these, triticonazole **3.91**, [131983-72-7] has been selected for its inhibition of *Tilletia caries*, *Septoria nodorum* and *S. tritici*, *Fusarium roseum*, *Ustilago nuda*, *Erysiphe graminis*, *Puccinia striiformis*, *P. recondita* and *Pseudocercospora herpotrichoides*. [3.744, 3.745, 3.746]



Triticonazole controls *Rhynchosporium secalis* on barley, *Sphacelotheca reiliana* on corn, *Rhizoctonia solani*, *Sclerotinia homeocarpa* and *Puccinia* on turf grass.[3.747, 3.748]

Similar cyclohexane compounds **3.92A** and **3.92B** also resemble the allyl substructure of the compounds described in section 3.7.4.



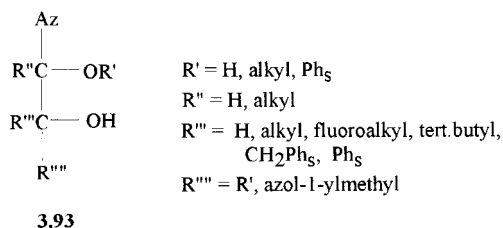
They show low fungicidal activity *in vitro*, but high activity *in vivo*, especially against *Sclerotinia sclerotium*, *Helminthosporium sativum*, *Fusicladium dendriticum* and especially *Erysiphe cichoracearum* on cucumber. O-Methyloximes **3.92A** are more active than nitrones **3.92B**. [3.749, 3.750, 3.751, 3.752]

A bicyclic analog, with tetramethylene connecting 5-C with 6-C of the cyclohexanol moiety, has been claimed as fungicide.[3.753]

3.8 1-(1,2-Dihydroxy-alkyl)-1H-azoles, their derivatives and analogs

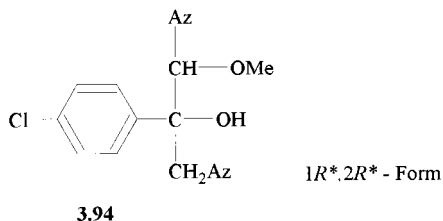
3.8.1 Monoderived 1-(1,2-dihydroxy-alkyl)-1H-azoles

Title compounds with the general formula **3.93** have been investigated extensively.[3.754, 3.755, 3.756, 3.757, 3.758, 3.759, 3.760, 3.761, 3.762, 3.763, 3.764, 3.765, 3.766, 3.767, 3.768, 3.769]



In one subgroup, the rare substituent $\text{R}' = \text{C}_6\text{H}_4-4-\text{CH}=\text{NOCH}_3$ has been specified [3.764, 3.765, 3.766, 3.767] A product with $\text{R}''' = -\text{C}_6\text{H}_3-2,4\text{F}_2$ has been claimed as an antimycotic of low toxicity for oral application.[3.768] Another related substance incorporates a second azole with $\text{R}''' = (1\text{H-azol-1-yl})\text{methyl}$. [3.761, 3.762, 3.768]

The best example appears to be **3.94** (Az = Tr), with an oral activity against mural candidiasis as strong as ketoconazole.[3.768]

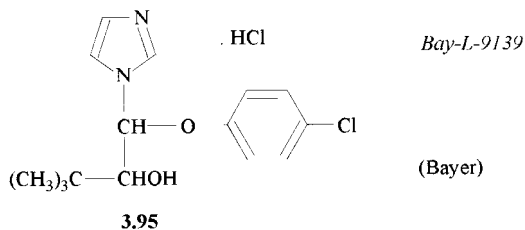


Separation into the optical isomers shows but little difference in this test.[3.770]

Other members of the title series have been found to control *Puccinia recondita*,[3.759] *Erysiphe graminis tritici* on wheat,[3.760] *E. cichoracearum* and *Sphaerotheca fuliginea* on cucumber.[3.754, 3.761, 3.762] Plant growth regulating activity has also been detected.[3.758]

Agents Bay-L-9139, triadimenol, bitertanol and BAS 110 .W have been developed from these series.

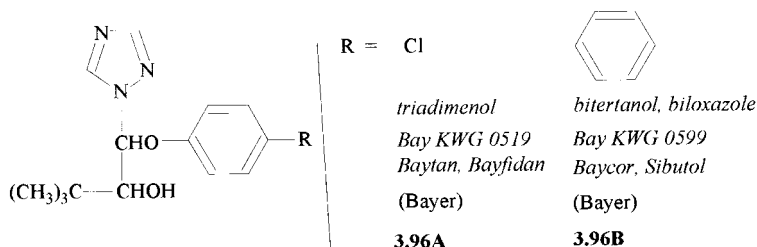
Compound **3.95**, Bay-L-9139 [base, 55362-18-0; (R*,R*-(±)-isomer, 80155-61-9] has been of some interest as an antimycotic.[3.771]



Its *threo*-stereoisomer can be obtained by a stereocontrolled reaction sequence.[3.772]

Bay-L-9139 has been demonstrated an antimycotic with *in vitro* activity against *Candida albicans*, *Candida* spp., *Cryptococcus neoformans*, *Coccidioides immitis* and dermatophytes, although of inferior activity compared with Bay-n-7133 (see section 4.9), to ketoconazole and miconazole,[3.771, 3.773] and to its precursor climbazole.[3.774] In contrast, efficacy rating against experimental vaginal candidiasis in the rat has arrived at ketoconazole > Bay-L-9139 > Bay-n-7133.[3.775, 3.776] Both of the latter are active p.o. against *Aspergillus* infections in animals.

Substance **3.96A**, triadimenol [55219-65-3, hydrochloride 80155-61-9], a systemic fungicide with protective and curative effects, has become the most investigated compound in this series.[3.777, 3.778] The (±)-*threo* form is prepared by stereoselective reduction of the respective ketone with aluminium isopropoxide or with NaBH₄ in aqueous NaOH/toluene [3.779, 3.780, 3.781, 3.782], with formic acid,[3.783] or with disodium dithionite.[3.784] It can also be obtained by resolution of the diastereoisomer mixture,[3.785] or by stereocontrolled synthesis from



the trans-oxirane with sodium 1,2,4-triazole.[3.786, 3.787] The reagent addition mode decides the preferred production of either *threo*- or *erythro*-form.

The crystal structure of triadimenol has been compared with that of paclobutrazole and diclobutrazole. The preferred solution conformer of (*RS*),(*SR*)-triadimenol is similar to the crystal conformer.[3.327]

Triadimenol on UV-photolysis in methanol produces 1-(4-chlorophenoxy)-3,3-dimethylbutan-2-one and 1-phenoxy-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.[3.788]

Triadimenol is known as metabolite of triadimefon (see section 4.7.2) through the action of fungi, e.g. *Fusarium culmorum*. For this reason, the tolerances of triadimenol and its metabolite 4-(4-chlorophenoxy)-2,2-dimethyl-4-(1H-1,2,4-triazol-1-yl)-1,3-butandiol,[3.789] have been ruled for animal forage.[3.790, 3.791]

Triadimenol seed treatment reduces powdery mildew disease on winter wheat and increases grain yield, [3.792] it controls *Pyrenophora tritici repentis* on spring wheat, *Erysiphe graminis tritici*, *Leptosphaeria nodorum* and *cochlibolus sativus*.

Triadimenol and bitertanol (see below) act as protectants and curative agents against powdery mildew on wheat and on barley,[3.794] and against leaf rust of the coffee plant.[3.795]. Triadimenol causes encapsulation of haustoria, so the uptake of nutrients by the fungus is reduced or stopped. Colonized cells undergo a hypersensitivity reaction and finally become necrotic, showing that the fungus also has stopped growing.[3.796] The center of action seems to be the complex between yeast cytochrome P-450_{14DM} and triadimenol.[3.797, 3.798]

Triadimenol may induce resistant populations e.g. of *Rhynchosporium secalis*, *Pyrenophora teres*, or *E. graminis hordei*. [3.799] This might be overcome by uneconomical measures like increased doses or more frequent dosing.

Triadimenol and its oxidation product triadimefon provoke hyperactivity in rats in contrast to twelve other structurally related pesticides, suggesting a rigid structure—activity relation for this CNS syndrome.[3.800]

The *threo*-form is more active than the *erythro*-form by a factor of 3—4 against *Calosporium cucumerium*, and by a factor of 8—32 against *Erysiphe graminis* f. sp. *hordei*. [3.801, 3.802] Absolute configurations of the four stereoisomers of triadimenol are given in Table 3.2.[3.803]

Table 3.2 Configurations of triadimenol (**3.96A**, KWG 0519) stereoisomers, their Bayer code and CA registry numbers.

(±)-Diastereoisomer I	KWG 0519A	[89482-17-7]
(±)-Diastereoisomer II	KWG 0519B	[82200-72-4]
(-)- <i>threo</i> 1S,2R	KWG 1522	
(-)- <i>erythro</i> 1S,2S	KWG 1523	
(+)- <i>threo</i> 1R,2S	KWG 1520	
(+)- <i>erythro</i> 1R,2R	KWG 1521	

Highest activity against *Rhizotania solani*, *Sclerotinia sclerotiorum*, *Cochliobolus miyabeanus*, *Pyricularia sasakii* and *Cercospora musae* is centered in the (-)-*threo* stereoisomer. The (+)-*erythro* form shows the weakest antifungal activity.[3.787]

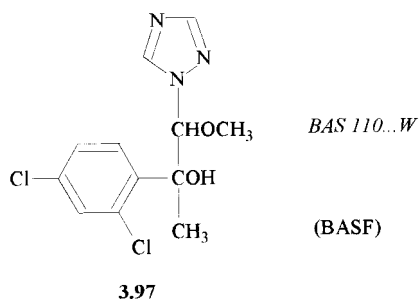
Compound **3.96B**, bitertanol [55179-31-2] represents a protective, curative and eradicated agro fungicide against diseases of the leaves.[3.804] This highly lipophilic agent penetrates plant surfaces readily, but is little transported inside or outside of the plant. It is distinctly different from triadimenol and triadimefon and shows higher activity against fungi imperfecti.[3.805, 3.806]

Bitertanol controls apple and pear scab, *Oidium* and *Monilinia laxa* on peaches, apricots, nectarines, cherries and prunes, *Sphaerotheca pannosa*, *Diplocarpon rosae* and *Phragmidium subcorticum* on roses, and *Erysiphe betae* and *Cercospora beticola* on sugar beet.[3.807] It is active against *Typhula blight* on barley.[3.794]

The fungitoxicity of the bitertanol enantiomers towards different strains of *Cladosporium cucumerium* differs by a factor of 1.8–8.2.[3.802] The 1S,2R-enantiomer displays the highest activity against *Uromyces phaseoli*. [3.805] For determination of residues, see.[3.808a]

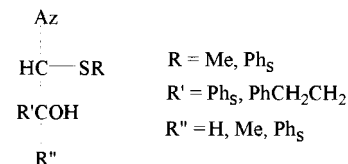
Compound **3.97**, BAS 110. W [83223-83-0], has been prepared as a diastereoisomeric mixture by the addition of CH_3MgCl to the respective ketone.[3.615, 3.787] High stereoselectivity can be achieved through chelate complexes.[3.809] BAS 110 W is mainly considered a plant growth regulator for crops like barley and oilseed rape; it decreases lodging and increases grain yield.[3.808]

However, BAS 110 .W also interferes with the sterol biochemistry in maize seedlings.[3.615]



3.8.2 1-(1-Thio-2-hydroxyalkyl)-1H-azole derivatives

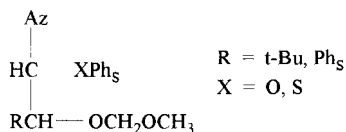
Monothio analogs **3.98** of the title formula have also been reported.[3.760, 3.763, 3.768]



3.98

Although their *in vitro* activity against *Candida albicans* and *Trichophyton asteroides* has appeared interesting, *in vivo* tests against murine candidiasis have been discouraging.[3.768]

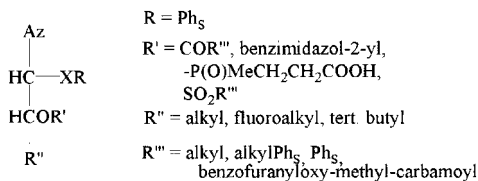
Similar compounds **3.99** control *Erysiphe graminis* and *Puccinia recondita* on wheat, and *E. cichoracearum* on cucumber.[3.810]



3.99

3.9 1-(1-subst. Phenoxy-2-hydroxy-alkyl)-1H-azole esters and carbamates

Title compounds like **3.100** have been claimed as fungicides.[3.811, 3.812, 3.813, 3.814,



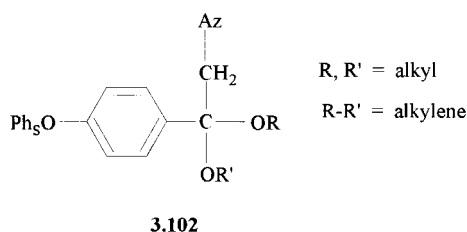
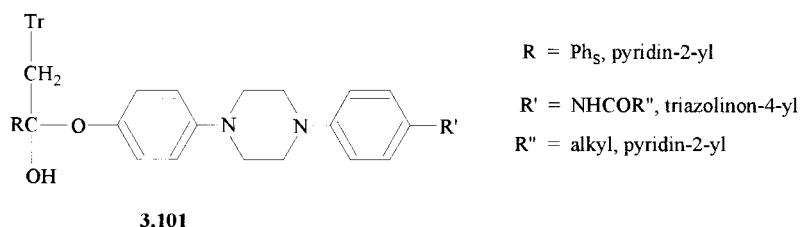
3.100

3.815, 3.816]

Some series include carbamates,[3.813, 3.816] esters of carboxylic,[3.812] phosphonic,[3.815] or sulfonic acids.[3.814] These substances protect apple seedlings

against attack from *Verturia inequalis*, tomatoes against *phytophthora*, and wheat seedlings against *Puccinia recondita*.

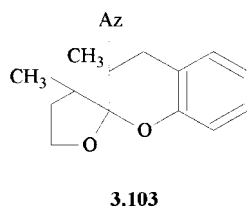
3.10 1-(2,2- and 3,3-Dihydroxy- and dithio-alkyl)-1H-azole semiketals and ketals



3.10.1 1-(2,2-Dihydroxyalkyl)-1H-azole semiketals and ketals

Title compounds with the general structure **3.101** (R' = H) constitute semiketals,[3.821] and those with R, R' ≠ H ketals **3.102**. [3.817, 3.818, 3.819, 3.820, 3.821]
(Claims for ketals sometimes also include dithioketals; see section 3.10.2).

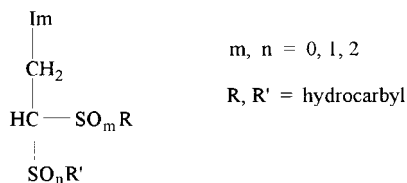
Ketals have been claimed as antimycotics inhibiting *Candida albicans* and as fungicides, e.g. for protecting wheat against *Puccinia graminis*.



Claims for non-cyclic forms of the title ketals often include cyclic forms, with R-R' standing for alkylene, thus forming e.g. dioxolanes or 1,3-dioxanes.[3.817, 3.818, 3.819] More compounds with these heterocycles are described in Chapter

6. Spiro forms **3.103** with plant growth-regulating activity have also been described.[3.822]

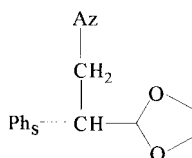
3.10.2 1-(2,2-Dithioalkyl)-1H-imidazole semiketals and ketals



3.104

Title compounds with the general structure **3.104**, which sometimes include oxygen ketals (section 3.10.1) have been claimed for their antimicrobial activity against *Candida*, *Trichophyton*, *Coriolus versicolor* and *Microsporum* fungi.[3.823, 3.824] Some also act as spermicides.

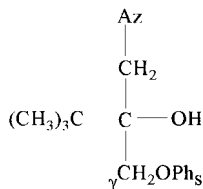
Substituents R and R' may be connected to form a five-to-seven membered ring.[3.824, 3.825, 3.826] Fungicidal activity against e.g. *Erysiphe cichoracearum* on cucumbers has been seen.



3.105

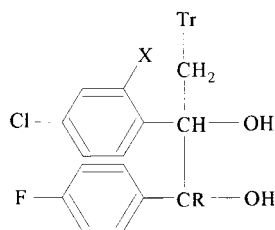
3.10.3 1-(3,3-Dihydroxyalkyl)-1H-azole ketals

Title compounds **3.105** have been claimed as fungicides.[3.827]



3.106

3.11 1-(x,y-Di- and x,y,z-Trihydroxyalkyl)-1H-azoles, their ethers, thioethers and analogs



X = H, Cl

R = H, CH₃, C₃H₇

3.107

3.11.1 1-(2,3-Dihydroxyalkyl)-1H-azoles and their ethers

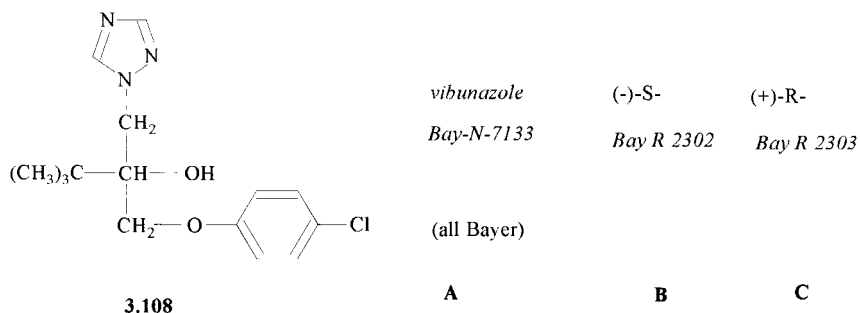
The title general structure **3.106** has been claimed for fungicides and plant growth-regulating agents in a great number of disclosures.[3.828, 3.829, 3.830, 3.831, 3.832, 3.833, 3.834, 3.835, 3.836, 3.837, 3.838, 3.839, 3.840, 3.841, 3.842, 3.843, 3.844, 3.845, 3.846, 3.847, 3.848, 3.849, 3.850, 3.851, 3.852, 3.853, 3.854, 3.855, 3.856, 3.857, 3.858, 3.859, 3.860, 3.861, 3.862, 3.863]

These compounds can be synthesized under enantiomeric control by a modified Sharpless asymmetric dihydroxylation to precursors of antifungals like Sch 45450 (see section 6.2.6). [3.864] Some of these compounds are also part of disclosures discussed in section 3.11.3. A full paper includes the optimization of structures **3.107**. [3.004, 3.865]

Best compounds **3.107** in the therapy of subacute systemic murine candidiasis agree in Az = Tr, R' = H and R'' = 4-F-C₆H₄-; [3.865] in some series R = triazol-1-ylmethyl is favored. [3.873]

Other claims are concerned with the synthesis of precursors, such as benzaldehyde—dialkylacetals, [3.874] or include the chromatographic separation of the diastereoisomeric esters with (+)-4-Cl-C₆H₄-CH(CHMe₂)COOH, followed by saponification, [3.846] or by asymmetric synthesis from chiral precursors. [3.861]

Compounds of this section show antifungal *in vitro* activity, e.g. against *Microsporum canis* and *Torulopsis glabrata*; they are effective in the oral treatment of



candidiasis and *Aspergillus fumigatus* infection of mice and display topical efficacy against *Trichophyton metagrophytes* infection of guinea pigs. Their fungicidal value has been demonstrated in their inhibition of *Puccinia recondita* and *P. graminis* on wheat, *Erysiphe graminis*, *Fusarium*, *Pyrenophora teres* and *Cochliobolus sativus* on barley, *Botrytis cinerea* on paprika, *Sphaerotheca fuliginea* on cucumber, *Pyricularia oryzae* on rice, and *venturia inaequalis*. Some also show plant growth-regulating properties.

From these series, vibunazole **3.108A**, [80456-55-9], Bay N-7133 has been developed as an antifungal agent and its stereoisomers Bay R 2302 and Bay R 2303 have been studied.[3.875]

Disclosures and papers report synthetic improvements of its preparation.[3.876, 3.877, 3.878]

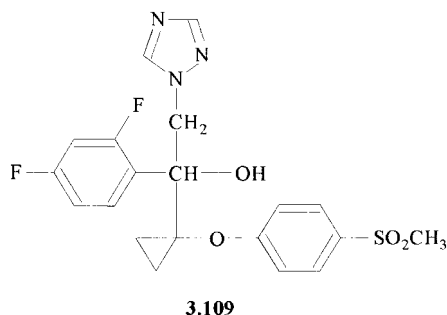
Optical resolution has been achieved by chromatographic separation of the d-(+)-camphor-10-sulfonates.[3.879, 3.880] Pure enantiomers, (-)-S-form **3.108B**, Bay R 2302, and (+)-R-form **3.108C**, Bay R 2303 have been synthesized. From these, Bay R 2302 is much more active against *Candida albicans*, *Torulopsis glabrata* and dermatophytes by a factor of 8–50 than R 2303. After oral administration to the rat, the mean plasma level of the nearly inefficient R 2303 is higher by a factor of 15 than that of the active enantiomer R 2302. However, the reverse is true for the beagle dog.[3.881]

Vibunazole presents an orally absorbed antimycotic with a broad-spectrum *in vitro* antifungal activity, comparable with that of ketoconazole and miconazole. The drug has been compared *in vitro* with ketoconazole as standard and with Bay-L-9139 (of section 3.8.1).[3.882, 3.883] No development of secondary resistance by a number of pathogenic fungi has been seen.

Antifungal activity of vibunazole has been demonstrated *in vivo* against systemic candidiasis in mice, but not in rats. It is endowed with a superior protective effect against *Aspergillois fumigatus* infection in mice compared with ketoconazole, which is encouraging for clinical application.[3.879] The drug is as active as ketoconazole against murine coccidiomycosis.[3.884]

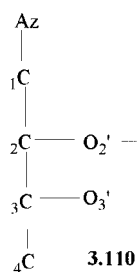
However, the agent has no clinically significant activity against *Aspergillus flavus*, *Scopulariopsis Zygomycetes* and *Sporothrix schenkii* isolates.[3.875]

Vibunazole and closely related substances have been recommended for the control of human and livestock diseases caused by *Herpes simplex* and cytomegalovirus.[3.885, 3.886] Its activity against *Fusarium* spp. isolates is unique.[3.887]

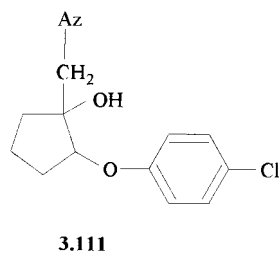


The pharmacokinetics of vibunazole has been studied in mice, rats, rabbits, beagle dogs and rhesus monkeys.[3.887] Bioavailability after oral dosing in dogs amounts to 70%.

In related series, cyclopropane is substituent at α -C.[3.861, 3.863, 3.866, 3.867, 3.868, 3.869, 3.870, 3.871, 3.872] An example is represented by **3.109** with good efficacy against systemic aspergillosis in mice.[3.863]

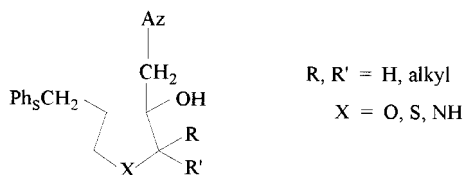


3.11.2 Cyclic and thio analogs of 1-(2,3-dihydroxyalkyl)-



1H-azoles

Only a few of all conceivable ways of connecting the numbered atoms of skeleton **3.110** by alkyl groups to arrive at non-spiro cycloalkanes, oxacycloalkanes or dioxacycloalkanes have been reported.

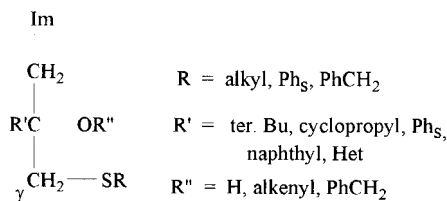


3.112

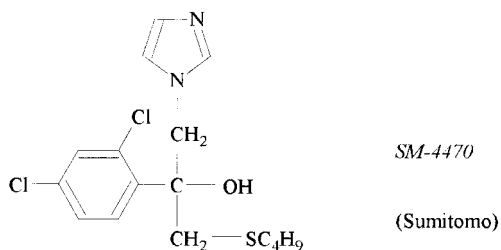
Connecting formally ${}_2\text{C}$ with ${}_3\text{C}$ by $-(\text{CH}_2)_n-$ with $n = 3$ yields cyclopentandiol **3.111**, [3.888] or with $n = 4$ cyclohexandiol. [3.889]

Connecting ${}_2\text{C}-$ with ${}_3\text{C}-{}_3\text{O}-$ by alkylen, $n = 2$ produces tetrahydrofuran-3-ols **3.112**, [3.890]

These substances inhibit *Pyricularia oryzae* and *Pyrenophora teres*.



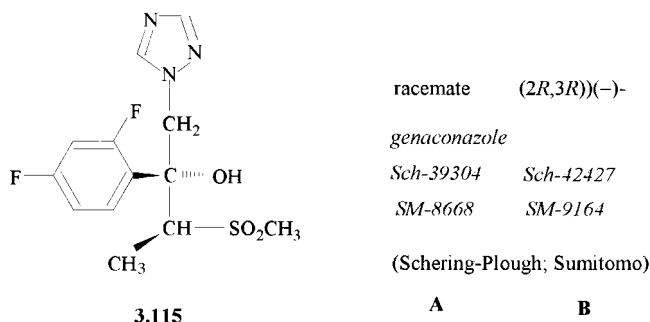
3.113



3.114

Connecting $_2\text{C-S-}$ with $_3\text{C}$ by *o*-phenylene yields 2-(1*H*-azol-1-ylmethyl)-3-hydroxy-2,3-dihydroisobenzothiophene derivatives, i. e. compounds **2.26A** to **2.26D**; see section 2.5.1.

Connecting formally $_3\text{C-}$ with $_3\text{C-S-}$ by trimethylene, arrives at 2-[2-(1*H*-azol-1-yl)-1-hydroxy-ethyl]tetrahydrothiofurans i.e. compound **6.35**; see section 6.1.11.



3.11.3 1-(2-Hydroxy-3-thio-alkyl)1*H*-azole derivatives

In a great number of disclosures, title compounds **3.113** have been claimed as antimycotics, fungicides and plant growth regulators.[3.891, 3.892, 3.893, 3.894, 3.895, 3.896, 3.897, 3.898, 3.899, 3.900, 3.901, 3.902, 3.903, 3.903a, 3.904, 3.905]

From these, substances SM-4470 and genaconazole have been investigated further.

For compound **3.114**, SM-4470 as (*R*)-enantiomer [89433-57-8] synthesis,[3.906, 3.907] and chiral preparations have been described.[3.908, 3.909]

SM-4470 is endowed with very high antifungal activity. It is twice as active as ketoconazole in the p.o. treatment of systemic candidal infection in mice.[3.910] Its efficacy in curing candidal vaginitis compared with ketoconazole is twice that in mice and equal to that in rats and guinea pigs.

The preparation of **3.115A**, genaconazole [120924-80-3] and closely related compounds is subject of numerous applications and papers.[3.911, 3.912, 3.913, 3.914, 3.915, 3.916, 3.917, 3.918, 3.919, 3.920, 3.921]

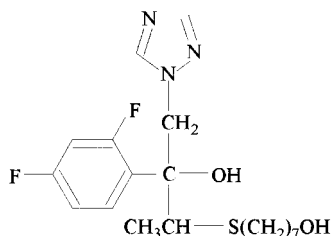
^{14}C -Labeled genaconazole has also been synthesized.[3.922]

Special efforts have been directed to receive pure enantiomers.[3.906, 3.909, 3.914, 3.915, 3.916, 3.918, 3.919, 3.920, 3.923, 3.924, 3.925, 3.926, 3.927, 3.928] The *in vitro* activity of the (2*R*,3*R*)-enantiomer Sch-42427, **115B** [121650-83-7] against *Candida albicans* is larger by a factor of 500 and against *A. fumigatus* by a factor of ca. 130 than that of the (2*S*,3*S*)-enantiomer.[3.921, 3.929] The superiority of Sch-42427 in the prophylactic treatment of infections of murines by the same fungi is distinguished by a similar factor.[3.921]

Genaconazole is more active than fluconazole in the control of *Fusarium solani* infections in mice.[3.911] It is active against murine pulmonary blastomycosis

sis,[3.930] and progressive coccidioidomycosis in humans. It shows action against cryptococcal meningitis in mice and invasive aspergillosis in immunosuppressed rabbits. Genaconazole is at least as effective as ketoconazole in the treatment of oropharyngeal candidiasis. It seems to be useful in the treatment of invasive mold infection in cancer patients.

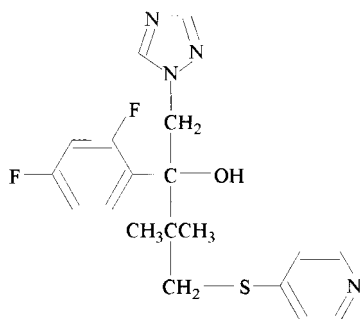
Parenteral compositions of genaconazole have been claimed.[3.931] The drug is well absorbed, little metabolized, and slowly eliminated.[3.932, 3.933] Pharmacokinetics of the two enantiomers mentioned above, after oral doses, are similar.[3.911] Enantiomer Sch-42427, is five times more potent than Sch 39304 in the treatment of murine cryptococcal and coccidioid meningitis, whereas Sch 42426 is only 1/50th as potent.[3.929, 3.933, 3.934] Sch 39304 is clearly superior on a mg/



3.116

kg basis in murine acute blastomycosis.[3.935]

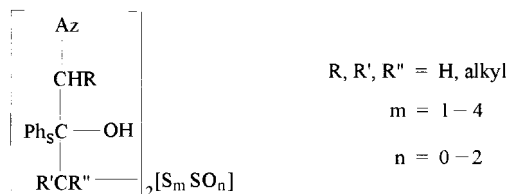
Against systemic *Candida albicans* infections, Sch 39304 is three times more active than fluconazole in mice, and 200 times more active than ketoconazole. In immunocompromized mice, the agent is 35 times more active than fluconazole. Genaconazole is also clearly superior to fluconazole in the treatment of systemic



3.117

Aspergillus flavus infections of mice.[3.936] The same is true for pulmonary *A. flavus* infections.[3.937] Sch 39304 does not seem to interfere with the action of oral contraceptives.[3.938]

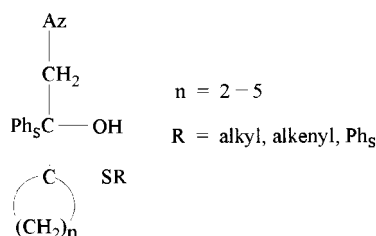
According to an *a priori* prediction by Multiple Computer-Automated Structure Evaluation, Sch 39304 has no likelihood of reproductive side effects.[3.172]



3.118

However, due to a carcinogenic potential, further clinical investigation was stopped.[3.939, 3.940]

Nonetheless, genaconazole is considered as a lead structure of great potential

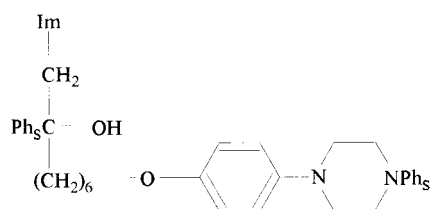


3.119

for new oral antimycotics and has been modified further by exchanging the SO_2CH_3 by SH or by hydroxyalkylthio. [3.941, 3.942, 3.943, 3.944] Thus, compound **3.116** is more efficacious than fluconazole against systemic aspergillosis in mice, while comparatively little hepatic enzyme induction has been seen. [3.942]

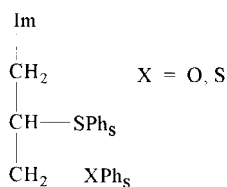
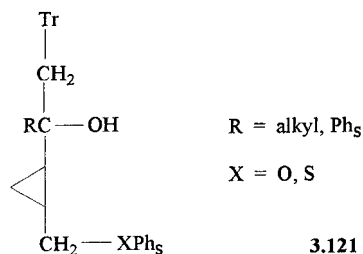
Further replacements of SO_2CH_3 have been carried out by cyanomethylthio, carboethoxyalkylthio,[3.941, 3.942, 3.943, 3.944, 3.945, 3.946] by arylthio, heteroarylthio or heteroarylmethylthio,[3.947, 3.948, 3.949, 3.950, 3.951, 3.952, 3.953, 3.954, 3.955, 3.956] The result is a potential antimycotic **3.117**, also with good efficacy against systemic experimental aspergillosis.[3.957]

Finally, genaconazole substituent SO_2CH_3 has been replaced by ethylsulfonyl or dimethylaminothiocarbonylthio,[3.958, 3.959] or by transformation into asym-



3.120

metrical or symmetrical disulfides such as **3.118**, [3.960, 3.961, 3.962] Many of these compounds have outstanding *in vivo* activity against *Candida albicans* infection of mice.

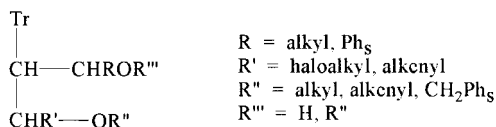


3.122

Returning to the title structure **3.113**, there are a number of claims for series **3.119** in which the γ -C is a member of a cyclopropane or a larger cycloalkane ring.[3.901, 3.963, 3.964, 3.965, 3.966]

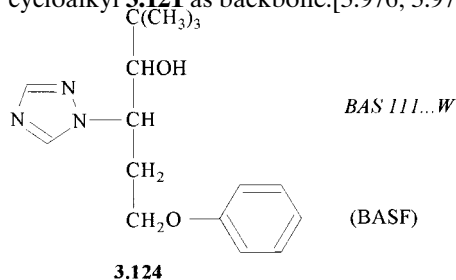
Some disclosures report the preparation of optical isomers by separation or chiral synthesis.[3.899, 3.908]

3.11.4 1-(2,x-Dihydroxy-alkyl)-1H-azoles and their thio and cyclic analogs



3.123

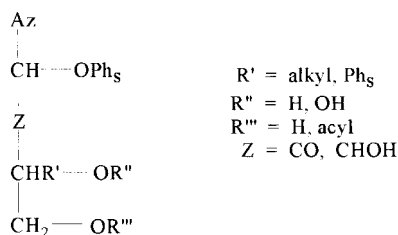
1-(2,x-dihydroxyalkyl)-1H-azoles **3.120** with $x > 4$ in the alkyl, have been claimed with noncyclic alkyl,[3.967, 3.968, 3.969, 3.970, 3.971, 3.972, 3.973, 3.974, 3.975] or with cycloalkyl **3.121** as backbone.[3.976, 3.977]



Compared with the structures of the previous section, the positions of -SH and -OH groups have also been reversed to 1-(2-thio-3-hydroxyalkyl)-azoles **3.122**. [3.924, 3.975, 3.978, 3.979] Structures like **3.122** show high antifungal activity.

Cyclic analogs, such as 2-benzyl-5-(hydroxyalkyl)-1H-azol-1-ylmethyl-1-cyclopentanols have been claimed as intermediates. [3.980]

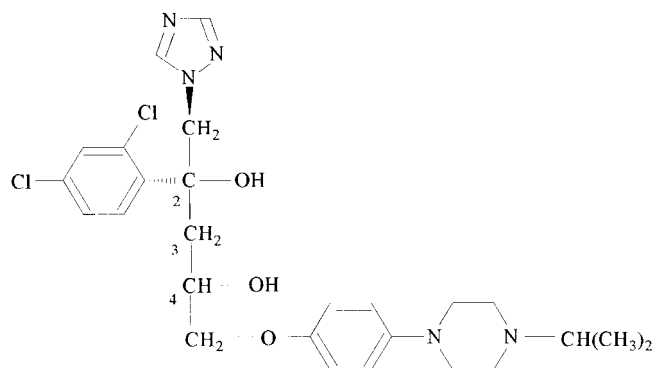
3.11.5 2-[(1H-Azol-1-yl)-1,x-dihydroxyalkanes and their thio analogs



3.125

Title compounds **3.123** have been claimed for their activity against *Trichophyton mentagrophytes* and *Botrytis cinerea*. [3.981, 3.982, 3.983, 3.984, 3.985, 3.986, 3.987, 3.988]

Compound **3.124**, BAS 111 .W [80553-79-3] from these series has been consid-



3.126

red mainly as a potential plant growth-regulator. [3.615]

A substance dihydro-PP969, prepared from the fungicide PP969 (see section 4.5.1), fitting into these structures, has still considerable antifungal activity. [3.989]

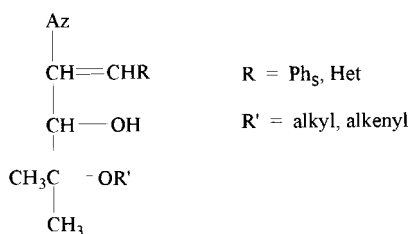
3.11.6 1-(x,y,z-Trihydroxyalkyl)-1H-azoles and their thio analogs

The general structure **3.125** represents claims for these potential fungicides.[3.990, 3.991, 3.992, 3.993, 3.993]

Compounds **3.126** represent derivatives of 1-(2,4,5-trihydroxyalkyl)-1,2,4-triazole which display 100% efficacy at 50 mg/kg p.o. in the treatment of *C. albicans* infected mice.[3.995]

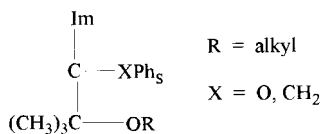
These substances also act as precursors for oxetans involving carbons 2, 3 and 4 (see section 6.2.4).

3.11.7 2-(x,y,z-Trihydroxyalkyl)-1H-azoles and their thio analogs



3.127

Title compounds have been claimed as antimycotics and fungicides, active against *Trichophyton mentagrophytes*, *Puccinia graminis* and *Botrytis cinerea*. [3.996, 3.997, 3.998]



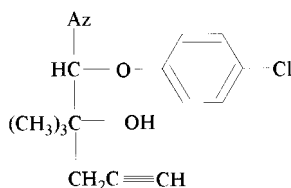
3.128

3.12 1-(Dihydroxyalkenyl)- and alkynyl)-1H-azoles

3.12.11(x,y-Dihydroxyalkenyl)-1H-azoles, their thio derivatives and cyclic analogs

Title structures can be divided into

- a) 1-(2,x-dihydroxy-1-(substituted alkyliden)-1H-azoles and derivatives like **3.127**, [3.999, 3.1000, 3.1001]
 b) 2-(1,x-dihydroxy)-1-alk-en-1-yl)-1H-azoles and derivatives and derivatives **3.128**, [3.1002, 3.1003, 1.004] and

**3.129**

- c) 1-/or 2-(1H-Azol-1-yl))x,y-dihydroxy-alk-z-enes.[3.1005, 3.1006]

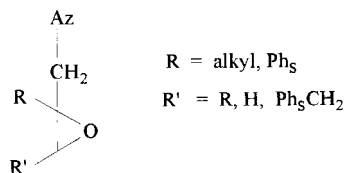
Activity against grain rust, *Erysiphe graminis tritici* on wheat, *E. Cichoracearum* on squash and plant growth regulation as well have also been reported.

(Cyclic analogs of the title compounds such as (1H-azol-1-yl)phenoxytetrahydrofuran-2-yliden methanols have been discussed in section 3.7.1).

3.12.2 x-(y,z-Dihydroxy-alkynyl-1H-azoles and derivatives

Title alkynyl derivatives **3.129** have been claimed as fungicides.[3.1007, 1.1008, 3.1009, 3.1010]

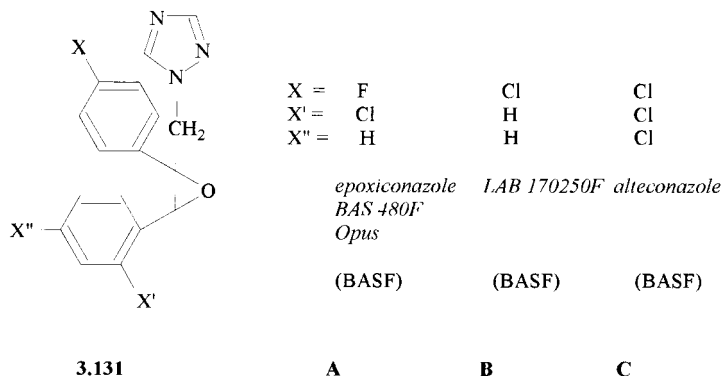
They inhibit *Erysiphe graminis hordei* and *Cochliobolus sativus* on barley.

**3.130**

3.13 1-(1,2-Oxidoethyl)-1H-azoles

A large series of title compounds **3.130** are presursors of the 1,2-dihydroxyalkyl- and 1,2-hydroxy-mercapto-alkyl-1H-azoles of sections 3.11.2 and 3.11.3, and of antifungal oxazolidines (see section 6.1.1), but they are also represent antifungals in their own right.[3.1013, 3.1014, 3.1015, 3.1016, 3.1017, 3.1018, 3.1019, 3.1020, 3.1021, 3.1022, 3.1023, 3.1024, 3.1025, 3.1026, 3.1027, 3.1028, 3.1029, 3.1030, 3.1031, 3.1032, 3.1033]

Most of this work has been done by BASF. Stereoisomers have been separated in many of the above series, and optically active precursors have been synthesized.[3.103, 3.1035, 3.1036] N-oxides have been prepared.[3.1037] One paper reports the synthesis of diazoly title compounds (R' , $R''' = Ph_s$, $R'' = 1-(1H-1,2,4-triazol-1-yl)methyl$);[3.1038] Precursors of the title compounds, 1-hydroxymethyl-1,2-di(subst.)phenyl-oxiranes have also been claimed.[3.1011, 3.1038]



Title epoxides show activity against bacteria and fungi pathogen to humans, and activity against *herpes simplex* infection of mice and guinea pigs. They control *Erysiphe graminis* and *Puccinia recondita* on wheat, wheat brown rust, *Plasmodiophora viticola* on grape leaves, *Botrytis cinerea* on paprika, and also display herbicidal action and plant growth regulation.[3.1017]

Out of these series, alteconazole, epoxiconazole and LAB 170250F have been selected for development.

Alteconazole, **3.131C** [93479-96-4] has been investigated as a potential fungicide, herbicide and virucide.

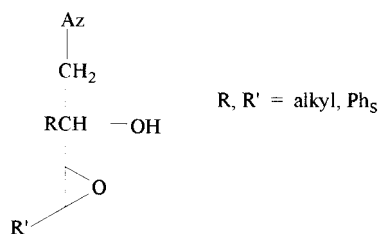
Epoxiconazole **3.131A** [106325-08-0] has been presented as a preventive and curative fungicide against Ascomycetes, Basidiomycetes, Deuteromycetes in cereals, sugar beet, peanuts, oilseed rape and ornamentals.[3.1040]

The four ^{14}C -isotopomers have been synthesized. [3.1041] Agricultural aspects, formulation, mode of action, toxicology, ecology and chemical development have been discussed.[3.1042, 3.1043, 3.1044, 3.1045, 3.1046] After application, effective adsorption to the plant surface leads to low losses during treatment and through rain.

Substance **3.131B**, LAB 170250F [88630-35-5], a strong fungicide, induces resistance in tobacco calli.[3.1047, 3.1048] It induces necrosis in the tips of maize leaves, and strongly decreases the Δ^5 -sterol content as evidence of its inhibition of P-450_{OBT.14DM} (obtusifoliol 14 α -methyl demethylase) from maize embryos.[3.615]

3.14 1-(x,y-Oxido-alk-z-enyl)-1H-azoles

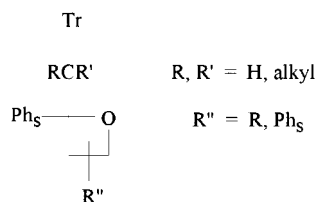
Title compounds have been claimed as antifungal agents and as precursors for these.[3.710, 3.1049]



3.132

3.15 w-(x-Hydroxy-y,z-oxidoalkyl)-1H-azoles

Title substances **3.12** have been claimed as agrochemical fungicides.[3.1050, 3.1051, 3.1052]



3.133

3.16 Azolymethyl-oxetanes

Title compounds **3.133** have been claimed as bactericides, antimycotics and fungicides.[3.1053, 3.1054, 3.1055, 3.1056, 3.1057]

They can be prepared from their 2,x-dihydroxyalkyl precursors (see section 3.11.4) and control e.g. *Pyricularia oryzae* and *Venturia inaequalis*.

(For azolymethyl-furanes and -pyranes, see sections 6.1.10, 6.1.12 and 6.2.4).

4 1-(Oxo-alkyl-, oxo-alkenyl, hydroxyalkylcarbonyl and dioxoalkyl)-1H-azoles and their derivatives

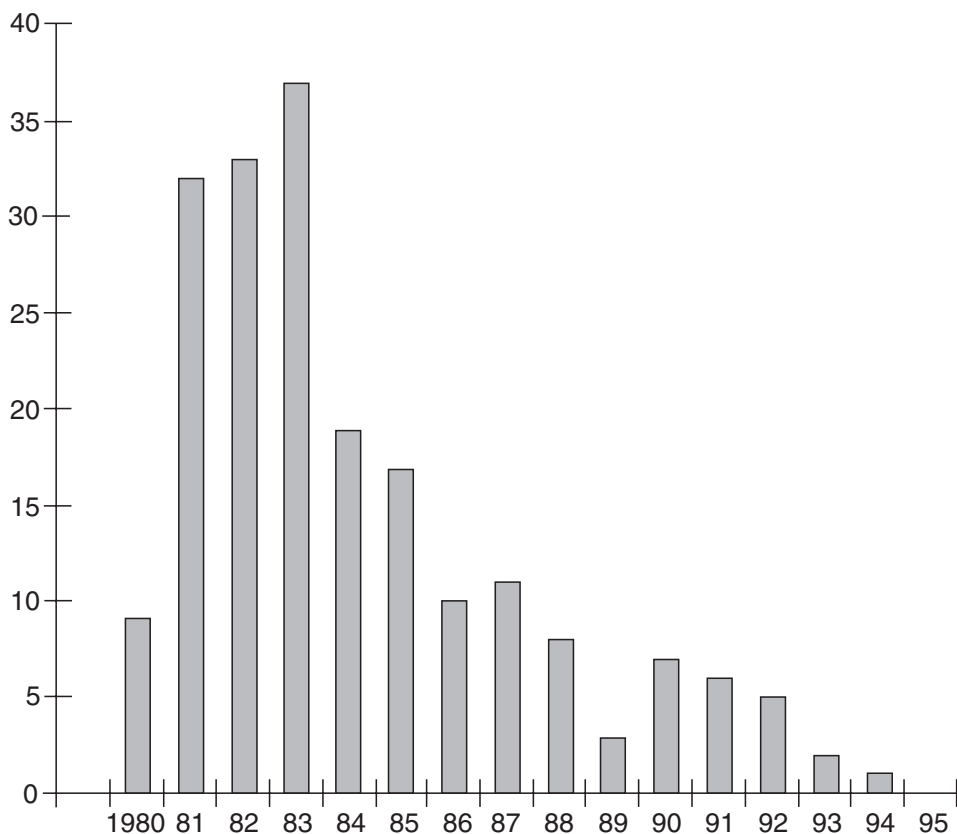
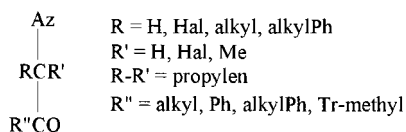


Fig. 4.1 Chronology of 200 patent applications of Chapter 4.

Compounds of this section frequently appear also in patent applications and papers as precursors of carbinols; see Chapter 3.

4.1 1H-Azol-1-ylmethyl-ketones

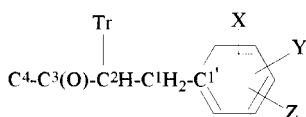
Azolylmethyl-ketones of the title structure **4.01** have been claimed as antimycotics for their inhibition of *Candida albicans*, *Trichophyton tonsurans* and *T. rubrum*, and as fungicides which control *Erysiphe graminis* on wheat, *E. graminis* sp. *hordei* and *tritici* on barley, *E. cichoracearum* on cucumber, *Podosphaera leucotricha* on apple leaves, *Piricularia oryzae* on rice plants, *Venturia inaequalis* and *Uncinula necator*. [4.001, 4.002, 4.003, 4.004, 4.005, 4.006, 4.007, 4.008, 4.009, 4.010, 4.011, 4.012, 4.013, 4.014, 4.015, 4.016, 4.017, 4.018]



4.01

A number of papers also report synthesis of these series, [4.019, 4.020, 4.021, 4.022, 4.023, 4.024, 4.025, 4.026, 4.027, 4.028] or discuss special reactions like α -halogenation. [4.029] A special group of compounds carries Az = 1H-pyrroles. [4.030] Another series includes a second triazolyl group (R' = Ph_s-C(Tr)H-). [4.031]

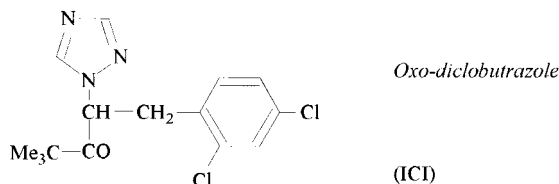
The synthesis of enantiomerically pure 2-bromoalkyl aryl ketones as precursors has been described. [4.032] A (RS)-mixture of a 2-(1H-triazol-yl-1-)-pentanon-3 has been separated by chromatography. [4.033] In 1-phenyl-2-(1H-triazolyl)-3-keto-alkanes crystallographic studies have shown that the C⁴ substituent and -C¹H₂C₆H₄X are *trans* to each other on a almost straight C³-C²-C¹-C^{1'} backbone **4.02**. [4.034]



4.02

C⁴ = part of phenyl or tert. Bu

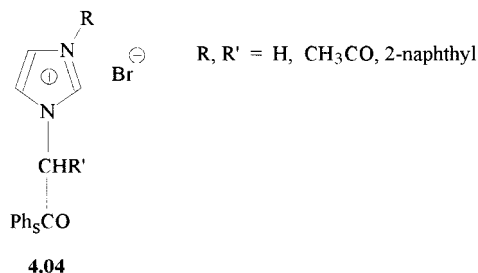
Of these compounds, oxo-diclobutrazole **4.03** is much less fungitoxic than diclobutrazole. [4.035]



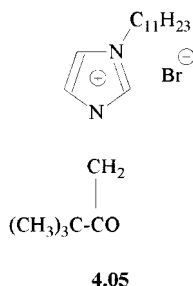
4.03

Metabolic reduction of ketone **4.03** is also negligible. Both observations have been explained with the absence of a factual or a potential enolic OH.[4.035]

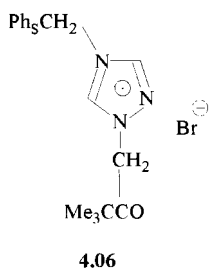
Imidazolium derivatives **4.04** with some microbicidal activity have been described.[4.036, 4.037, 4.038]



Among these, compound **4.05** is more active than paclobutrazole (section 3.2.3.1).

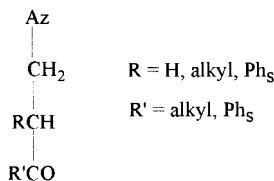


4*H*-1,2,4-triazolium compounds **4.06** rearrange in the presence of NaH/DMF to 4-amino-1-subst. benzyl-5-acyl-imidazoles.[4.039]



4.2 2-(1*H*-Azol-1-yl)-ethyl-ketones

Some disclosures,[4.040, 4.041, 4.042, 4.043] and papers,[4.044, 4.045, 4.046, 4.047, 4.048, 4.049] report the synthesis of title substances **4.07**.

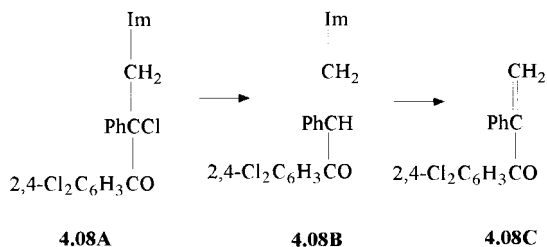


4.07

Substances **4.07** represent potential bactericides which inhibit *Clostridium perfringens*, *Bacteroides fragilis*, *Propionibacterium acnes* and other anaerobic bacteria e.g. in periodontal disease. They act as antimycotics, and as fungicides which control *Scirpus hotarui* on rice and *Erysiphe graminis hordei*.

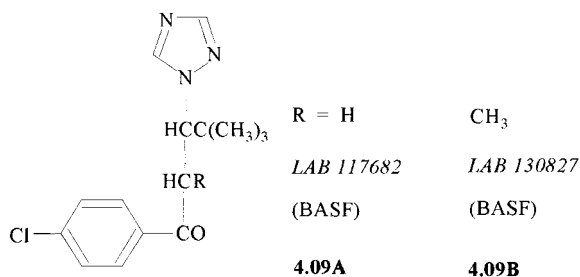
In related cyclic compounds substituents R' and R form part of a tetrahydrocarbazolone.[4.050] Others carry a second azole group in place of R'.[4.051]

Agent **4.08A** is reduced to **4.08B** and further broken down to **4.08C** by anaerobic organisms.



All three substances have similar activity against these bacteria, but **4.08C** is very unstable.[4.047, 4.048]

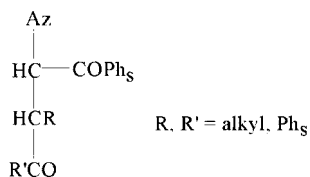
Two compounds studied in detail are **4.09A**, LAB 117682 [7005-75-3] and **4.09B**, LAB 130827 [77666-25-2] which display outstanding plant-growth retarding activity.[4.052]



Torsion angles have been derived from the crystal structure of analogs based on a 2-(1H-triazol-yl)pentane-3-one backbone.[4.034]

4.3 *x*-(1*H*-Azol-1-yl)alkyl-*y,z*-diketones

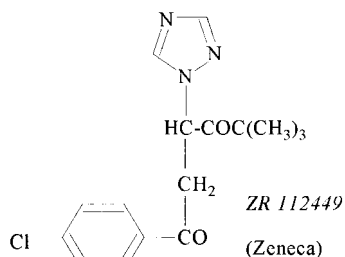
Title diketones **4.10** have been claimed as fungicides.[4.034, 4.053, 4.054]



4.10

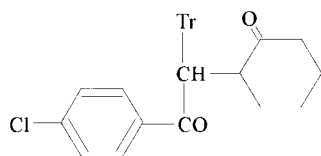
During synthesis their isomeric enol phenacylestere (see section 3.7.2) are also formed.[4.055] This product mixture protects cucumbers against *Sphaerotheca fuliginea*, and inhibits *Erysiphe graminis* and *Puccinia graminis* on wheat.[4.034]

Compound **4.11**, ZR 112449, a plant growth regulator, has been prepared in a ^{14}C -labeled form.[4.056]



4.11

A cyclic analog of these compounds is depicted by **4.12**, which controls oidium on cucumber caused by *Sphaerotheca fuliginea*. [4.057]

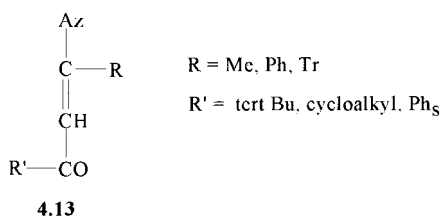


4.12

4.4 x-(1H-Azol-1-yl)-1-alkene-y-ones

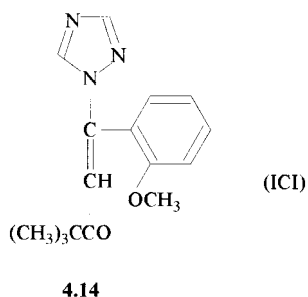
4.4.1 1-(1H-Azol-1-yl)-1-alkene-3-ones and cyclic analogs

Title compounds **4.13** have been claimed as inhibitors of nitrification.[4.058]

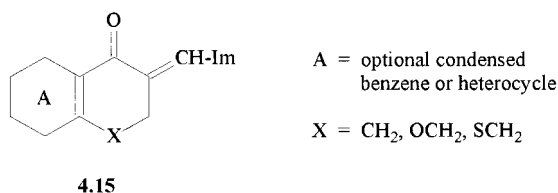


The chemistry of these compounds (with R = Me, Ph; Az = Im) has been extensively studied,[4.059, 4.060, 4.061, 4.062, 4.063, 4.064, 4.065, 4.066, 4.067] also those with quaternized imidazole.[4.059, 4.068, 4.069]

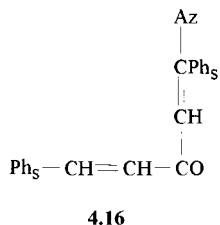
Compound **4.14** of these series has been demonstrated as inhibitor of sterol synthesis in tobacco plants at the 14 α -methyl demethylation step, and compared with LAB 170250F (of section 3.13).[4.070]



Some cyclic analogs like **4.15** show activity against *Candida krusei* and moderate inhibition of *C. albicans* and *Trichosporon beigeli*.[4.071]

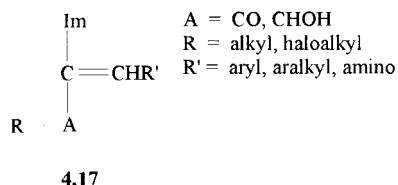


Azoly-divinylketones **4.16** are the subject of two papers.[4.072, 4.073]



4.4.2 2-(1*H*-Azol-1-yl)-1-alken-3-ones

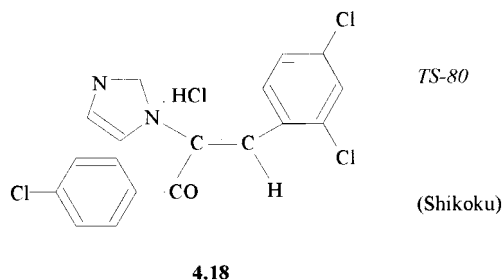
Title compounds of the general structure **4.17** have been claimed often as antimycotics and fungicides.[4.074, 4.075, 4.076, 4.077, 4.078, 4.079, 4.080, 4.081, 4.082, 4.083, 4.084, 4.085, 4.086, 4.087, 4.088, 4.089, 4.090, 4.091, 4.092] They are also the subject of several papers.[4.093, 4.094, 4.095, 4.096]



Some sulfonyl ketone bromides have been claimed as intermediates.[4.097]

(*E*)-isomer content, which generally includes the main microbiocidal activity, can be increased by heating the (*Z*)-isomer with PhSNa , [4.075, 4.076] with toluene sulfonic acid, [4.077] with $3\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$, [4.098] with a secondary amine, [4.087, 4.099] or with a sulfuric acid—bromine mixture. [4.090, 4.100] Monohydrogen sulfate salts have been prepared and used to increase stereoisomeric purity. [4.101, 4.102, 4.103, 4.104]

Activity has been demonstrated against *Candida albicans*, *Trichophyton rubrum*, *T. tonsurans* and *Microsporum gypseum*. In one series, nine out of 37 compounds displayed excellent *in vitro* inhibition of *C. albicans*, *A. fumigatus* and *T. asteroides* compared with e.g. clotrimazole and miconazole, but have been disappointing on a p.o. doses basis against subacute systemic infection of mice. [4.093] Substance **4.18**, TS-80 has been submitted for clinical trials. [4.105]

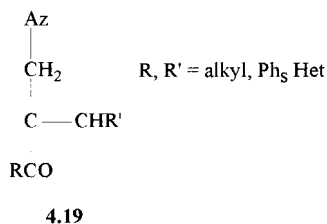


More such compounds with excellent activity against Gram-positive bacteria and fungi carry 3,4-Cl₂ or 2,3,5-Cl₃ substituents on the 3-phenyl group.[4.106]

A number of these substances also show plant growth inhibitory properties.[4.101, 4.103, 4.104]

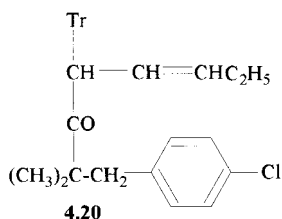
4.4.3 2-(1H-Azol-1-ylmethyl)-1-alken-3-ones

Title compounds **4.19** have been claimed as agricultural fungicides which inhibit ascomycetes and basidiomycetes.[4.107]



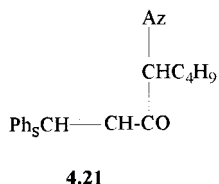
4.4.4 3-(1H-Azol-1-yl)-1-alken-4-ones

Title compounds like **4.20** have been claimed as fungicides and plant growth regulators.[4.108]



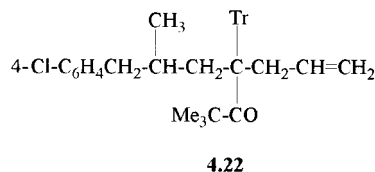
4.4.5 4-(1-H-Azol-1-yl)-1-alken-3-ones

Title compounds like **4.21** act as bactericides and antimycotics.[4.109]



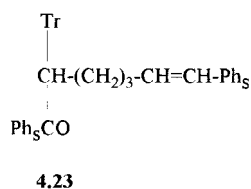
4.4.6 4-(1H-Azoly-1-yl)-1-alken-5-ones

Title compounds like **4.22** control brown rust on wheat.[4.110]



4.4.7 6-(1H-Azol-1-yl)-1-alken-7-ones

Fungicidal title compounds **4.23** have been reported in a paper.[4.111]

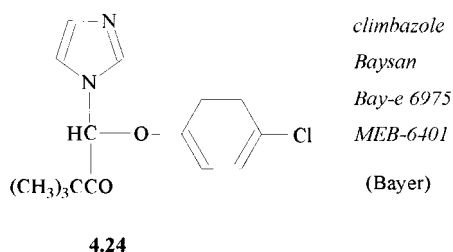


4.5 1-(1H-Azol-1-yl)-x-hydroxyalkan-y-als or -ones and derivatives

4.5.1 1-(1H-Azoly-1-hydroxy)alkan-2-one ethers

4.5.1.1 1-(1H-Imidazolyl-phenoxy)alkan-2-ones

Climbazole **4.24**, [38083-17-9] presents the most prominent of the title compounds.[4.112, 4.113]

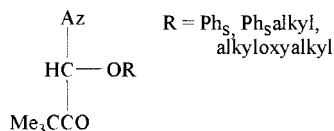


In contrast to triadimefon (see section 4.5.1.2), climbazole is not reduced by fungi, e.g. *Cladosporium cucumerinum* to the carbinol, suggesting that the unmetabolized drug is the fungitoxic agent.[4.114] Indeed, the reduced climbazole (Bay-L 9139 [55362-18-0] (see section 3.8.1) is less fungitoxic. Thus, it appears that climbazole acts as a fungicidal agent through its enolic form.[4.114]

Climbazole inhibits *Aspergillus*, *Penicillium*, *Candida* and *Poecilomyces* fungi on household apparel, which recommends its use as household fungicide.[4.115] It is also useful as a component part of anti-dandruff shampoos,[4.116] and in dental mouthwashes to combat gingivitis and periodontitis.[4.117]

4.5.1.2 1-(1H-Triazolyl-1-phenoxy)alkan-2-ones and analogs

Title compounds of the general structure **4.25** have been claimed as antimycotics, fungicides and some also as plant regulators.[4.118, 4.119, 4.120, 4.121, 4.122, 4.123, 4.124, 4.125, 4.126, 4.127, 4.128, 4.129, 4.130, 4.131]

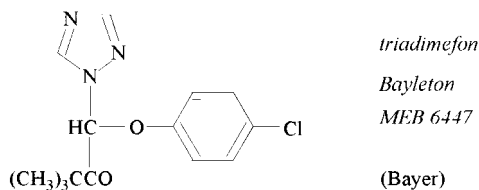


4.25

Their complexes with divalent metals such as Cu, Mg, Mn and Zn have also been claimed as fungicides. [4.128]

In the title compounds, antimicrobial activities have been observed against *Pyricularia oryzae* on rice, *Sphaerotheca fuliginea* on cucumber, *Colletotrichum* spp., *Leptosphaeria nodorum* on wheat and *Podosphaera leucotricha* on apple trees.

From these substances, compound **4.26**, triadimefon [43121-43-3] has been selected.[4.132, 4.133, 4.134]



4.26

One-pot syntheses of triadimefon have been described, [4.135] one using PTC,[4.136] and synthetic methods have been reviewed.[4.137] The crystal structure has been determined.[4.034]

Triadimefon and other closely related substances have been subjected to a Hansch QSAR study based on MIC values against *Saccharomycopsis lipolytica* in the agar diffusion test and on 50% inhibition value of ergosterol synthesis in the

same yeast.[4.138] Both data series are well correlated in Spearmans rank, but only moderately connected to electronic parameters F and R.

Triadimefon, which consists of a racemic mixture of (-)- and (+)-isomers,[4.133] displays its antifungal activity through its reduction product triadimenol. This transformation can be effected by the plant under treatment, or by a fungus. Different qualitative and quantitative combinations of the four possible enantiomers are formed by *Coriolus versicolor*, *Cladosporium cucumerium*, *Botrytis cinerea*, *Rhizoctonia solani* or *Fusarium culmorum*. [4.139, 4.140]

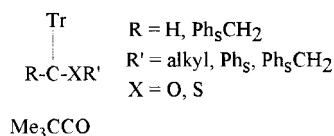
The agent provides both protective and curative control against *Erysiphe graminis*, *Rhynchosporium secalis*, *Septoria tritici* and rust diseases of cereals and against many fungal diseases of stone fruit, hop, vine, coffee, soja, tobacco, sugar cane and beet and on ornamental plants. It shows prominent activity via the gas phase.[4.132] Triadimefon inhibits *Coniophora puteana*, *Coriolus versicolor* and *Pori monticola* and has therefore been recommended for the preservation of wood.[4.141]

The fungal toxicity of triadimefon is antagonized by Paraquat bis(methyl sulfate).[4.142] No stable resistance of *Erysiphe graminis tritici* against triadimefon has been detected.[4.143]

In addition, triadimefon displays plant growth regulatory effects, especially on dicotyledoneous plants. Tolerances of triadimefon residues and its metabolites have been established.[4.133, 4.144, 4.145, 4.146]

4.5.1.3 1-(1H-Azol-1-yl-1-hydroxy)alkan-2-ones, their thio analogs and derivatives

Title compounds **4.27** have been claimed as bactericides, fungicides and plant growth regulators. [4.147, 4.148]

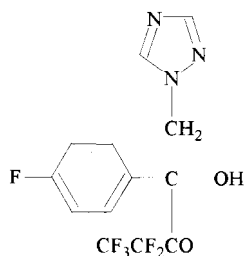


4.27

Derivatives include esters ($\text{XR}' = \text{OCOR}''$; $\text{R}'' = \text{Ph}_5, \text{Ph}_5\text{CH}_2, \text{Ph}_5\text{OCH}_2$). [4.149, 4.150, 4.151, 4.152]

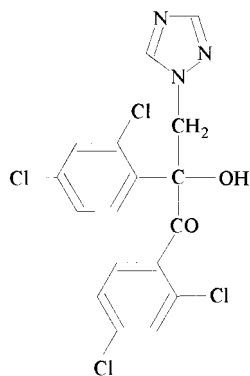
4.5.2 1-(Azol-1-yl)-2-hydroxyalkan-x-ones

Title 1-(azol-1-yl)-2-hydroxyalkan-3-ones **4.28** inhibit *in vivo* dermatophytes, *Candida albicans* and act as fungicides e.g. against *Cochliobolus sativus*, and *Sphaerotheca fuliginea* on cucumbers.[4.153, 4.154, 4.155]



4.28

Thirteen out of 76 of these compounds have demonstrated interesting *in vitro* antimicrobial activity and excellent therapeutic effect on subacute systemic murine candidiasis.[4.155] After additional tests against guinea pig dermatophytosis, compound **4.29** remained as optimum with a demonstrated superiority over ketoconazole.



4.29

The synthesis of its optical isomers has been studied.[4.156]

Title 1-(azol-1-yl)-2-hydroxyalkan-4-ones **4.30** have been claimed as fungicides and plant growth regulators.[4.157]

Az

CH₂

RC—OH R = alkyl, Ph₅

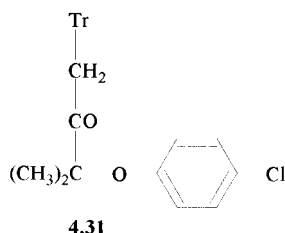
R'-CH R', R'' = H, R

R''CO

4.30

4.5.3 1-(Azol-1-yl)-3-hydroxy-2-ketone ethers

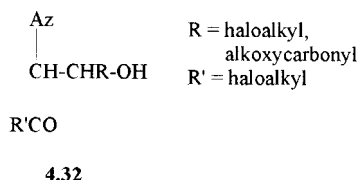
Title 1-(1H-azol-1-yl)-3-hydroxyalkan-2-ones like **4.31** have been disclosed as fungicides.[4.158]



4.6 2-(1H-Azol-1-yl)-x-hydroxy or x,x'-dihydroxyalkane-y-ones, their thio analogs and derivatives

4.6.1 2-(1H-Azol-1-yl)-1-hydroxy-alkan-3-ones and their thio analogs

Title compounds of the general structure **4.32** have been described in patent applications and papers.[4.159, 4.160, 4.161, 4.162]

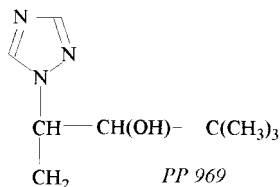


Activity has been demonstrated against *Erysiphe graminis* on barley.

4.6.2 2-(1H-Azol-1-yl)-1-hydroxyalkan-4-ones

From these series, compound **4.33**, PP969 [69141-50-0] has been selected for further investigation.[4.163, 4.164, 4.165]

The main activity of this systemic agent against foliar fungal diseases, either by foliar or by stem application, rests in the (*R**,*R**)-(±)-enantiomer. The high water solubility of 3.6 g/L is 28 times larger than that of fluotriafol (see section 3.2.2.5).



PP 969

 $(\text{CH}_3)_3\text{C-CO}$

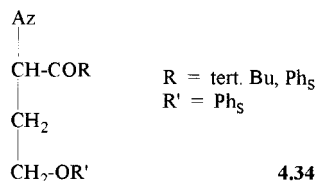
(ICI)

4.33

Due to its mobility in woody plants, PP969 shows excellent activity against *Erysiphe graminis hordei*, *E. gr. tritici*, *Puccinia recondita*, *Venturia inaequalis* and *Podosphaera leucotricha* on apple, *Uniclinula necator*, and *Cercospora arachidicola*. [4.166] The agent protects apple seedlings against *Nectria galligena* surpassing the efficacy of bitertanol and triadimenol.[4.163] It also controls *Homileia vastatrix* on coffee and *Mycosphaerella musicola* on bananas.[4.164]

4.6.3 2-(1H-Azol-1-yl)-4-hydroxyalkan-1-one ethers

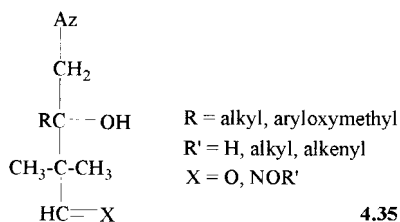
The title series **4.34** has been claimed.[4.166]



4.34

4.6.4 1-(Azol-1-ylmethyl)-1,2-dihydroxy-alkyl 3-aldehyde derivatives

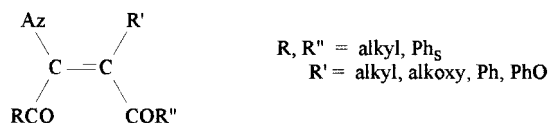
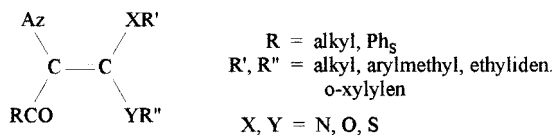
Title compounds exemplified by general structures **4.35** show *in vivo* antimycotic activity against dermatophytes and candidas and also control *Cochliobus sativus*. [4.167, 4.168]



4.35

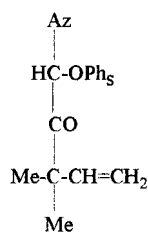
4.7 1-(1,2-Diacylvinyl)azoles, 1H-azolyl-vinyldiacetals, and -thioketals

Title ketones with the general structures **4.36**, related paraffinic and olefinic homologs,[4.169] their thioketals,[4.170, 4.171] ketenacetals and amins **4.37**,[4.172] have been claimed as fungicides and plant growth regulators.

**4.36****4.37**

4.8 1-(1H-Azol-1-yl)-1-hydroxyalkyl-3-ketones with other functions in α' -position

Title compounds **4.38** with additional olefinic, alkylthio or phenoxy substituents have been claimed as antimycotics and fungicides.[4.173, 4.174, 4.175, 4.176, 4.177]

**4.38**

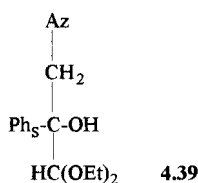
Antimycotic action has been demonstrated with infected mice. Inhibition of *Leptosphaeria nodorum* on wheat and *Podosphaera leucotricha* on apple trees has been seen.

For related homologs of title compounds, see section 4.10.3.

4.9 1-(1H-Azol-1-yl)-2-hydroxyethylz-aldehydes or -ketones, their ethers and thio analogs

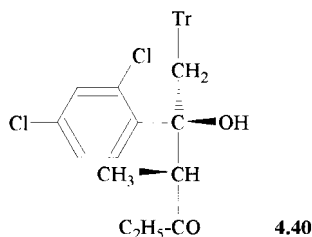
4.9.1 1-(1H-Azol-1-yl)-2-hydroxyalkyl 3-aldehyde acetals

Title compounds **4.39** have been claimed as fungicides and plant growth regulators.[4.178]

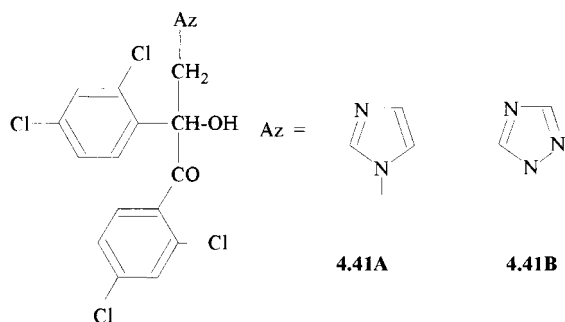


4.9.2 1-(1H-Azol-1-yl)-2-hydroxyethyl-3-ketones

One title substance **4.40** presents its main activity in the less polar *2RS,3RS* diastereomer. [4.179]



Imidazole compound **4.41A** has been claimed as antimycotic with high *in vitro* activity against *Trichophyton asteroides*, and fungicidal action against *Sphaerotheca fuliginea* on cucumber.[4.180]

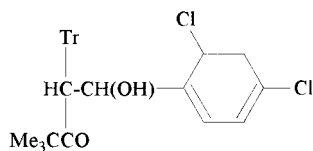


The triazole analog **4.41B** in its (*R*)-(-)-configuration has been demonstrated as the more active stereoisomer in the murine candidiasis model of the mouse.[4.181]

4.10 x-(1H-Azol-1-yl)-1-hydroxyalkyl/ or 1-hydroxyalkenyl-z-ketones

4.10.1 2-(1H-Azol-1-yl)-1-hydroxyalkyl-3-ketones

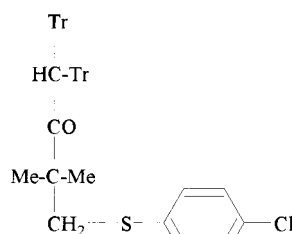
Title compounds like **4.42** control e.g. *Erysiphe graminis* on barley, and show plant growth-regulating activity as well.[4.182, 4.183, 4.184, 4.185, 4.186]



4.42

4.10.2 x-(1H-Azol-1-yl)-1-hydroxyalkyl-z-ketones

Title compounds with Az at ₃C to ₉C of the alkyl, as in example **4.43**, have been claimed as fungicides which inhibit *Pyricularia oryzae* and *Erysiphe cichoracearum*. [4.187, 4.188, 4.189]

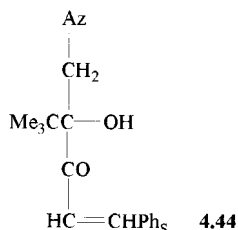


4.43

These structures may also carry a second heterocyclic ring such as 1,2,4-triazole or dioxane.

4.10.3 x-(1H-Azol-1-yl or 1H-azol-1-ylmethyl)-1-hydroxyalken-3-yl-z-ketones

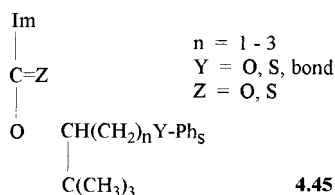
Title compounds, e.g. **4.44** have been claimed as fungicides with activity against *Pyricularia oryzae*. [4.190, 4.191]



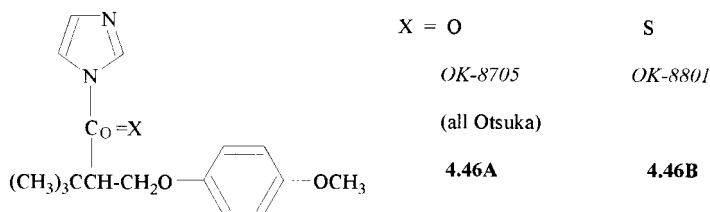
4.11 1H-Azol-1-yl-carboxylic acid and -alkyl-carboxylic acids and derivatives

4.11.1 1-(1H-Azol-1-yl)-carboxylic and thiocarboxylic acid derivatives

A few claims have been filed for title compounds **4.45** as antimycotics and fungicides. [4.192, 4.193, 4.194, 4.195, 4.196]



Structure—activity relations have been studied using inhibition of *B. cinerea* and *Giberella fujikuroi*, octanol—water coefficient P, lipophilic parameter π and also hydrolytic and photolytic stabilities, with optimal compounds **4.46A**, OK-8705 [(±)-, 56764-91-9] and **4.46B**, OK-8801 [(±)-156764-92-0]. [4.196, 4.197, 4.198]



Thiocarboxylates are stable to hydrolysis, but less stable to light; the photostability is closely associated with the in-plant availability of these agents. However, stability half-lives have been found that are lower than that of the standard, prochloraz. In conclusion, the carboxylates seem preferable to the thiocarboxylates.

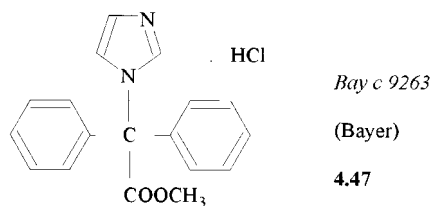
Selected compounds OK-8705 and OK-8801, mainly as their (*R*)-enantiomers, display *in vitro* activity against *Botrytis cinerea*, *Gibberella fujikuroi* and *Sphaerotheca fuliginea*, and control mildew on cucumber seedlings.

(1-(1H-Azol-1-yl)-carboxamides are considered as analogs of urea; see section 5.4).

4.11.2 x-(1H-Azol-1-yl)-alkyl-carboxylic acids, esters and amides

2,5-Diphenyl-1-pyrazoleacetic acids inhibit bacteria.[4.199]

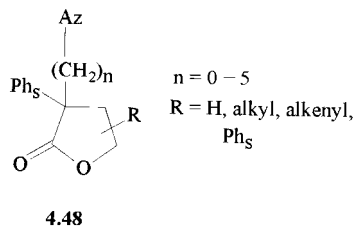
The imidazole derivative **4.47**, Bayer-c 9263 [56290-29-0] shows broad spectrum-antifungal activity with relatively low MIC values, and is effective against fungal diseases in mice.[4.200, 4.201]



However, this substance is only moderately absorbed its and half-life is also insufficient. Its metabolites are also active against fungi.

2-Aryl-3-chloro-3-(1,2,4-triazol-1-yl)propionic acid esters protect wheat from *Erysiphe graminis*. [4.202]

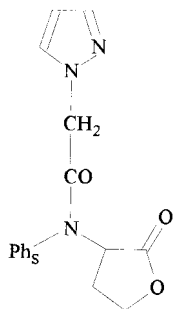
Cyclic esters **4.48** control powdery mildew on beans.[4.203]



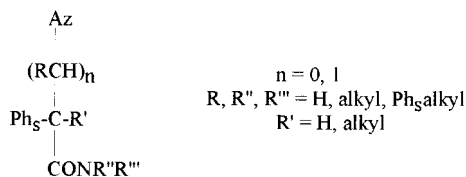
1- and 2-Tetrazolylacetic acids also have antibacterial activity.[4.204, 4.205]

1,2-Pyrazol-1-ylacetamides **4.49** have been claimed as fungicides.[4.206, 4.207]

Carboxylic acid amides of the general structure **4.50** control, after oral doses, *Candida albicans* infections in mice.[4.208, 4.209, 4.210, 4.211, 4.212, 4.213, 4.214, 4.215]



4.49



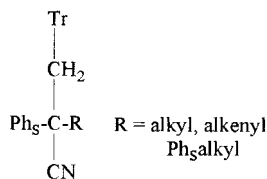
4.50

These compounds inhibit Gram-positive and Gram-negative bacteria.[4.214] They control *Erysiphe graminis* on barley, *Pseudoperonospora cubensis*, and *Pellicularia filamentosa* on rice seedlings.

Imidazole 3-oxides of the title compounds have been claimed as plant virucides.[4.216]

4.11.3 1H-Azol-1-yl-alkyl-nitriles

Title compounds **4.51** have been claimed as antimycotics and fungicides.[4.217, 4.218, 4.219, 4.220, 4.221, 4.222, 4.223, 4.224, 4.225, 4.226, 4.227]



4.51

Some nitriles are part of the claims for the corresponding carboxylic acid derivatives in section 4.11.1.

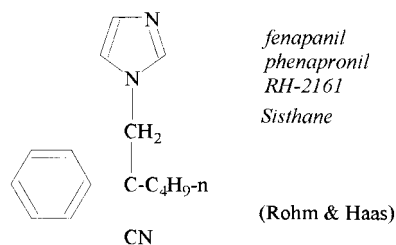
Trimellitic acid salts of the title compounds have been prepared.[4.220, 4.228]

These nitriles, after p.o. doses, protect mice infected with *Candida albicans*. They also control *Puccinia recondita* and *Erysiphe graminis* on wheat seeds, *Pyri-*

cularia oryzae, and *Helminthosporium oryzae*. Some are toxic against *Aspergillus niger* and *Aureobasidium pullulans*, which makes them suitable for the preservation of wood.[4.226] Another series of nitriles also shows plant growth regulation.[4.227]

From the title series, fenapanil, fenbuconazol, myclobutanil and RH 5781F have been developed.

Fenapanil **4.52** [61019-78-1], has been marketed under Sisthane, which must not be confused with Systhane—the trademark for myclobutanil.[4.230]



4.52

Fenapanil was used against scab and powdery mildew on pome fruits, against *Pyrenophora graminea*, and for cereal seed treatment, but it also inhibits the roots and shoots of barley seedlings.[4.229]

Though fenapanil had to be succeeded,[4.231] the strategy followed for its discovery is interesting.

Eventually, the molecular development of **4.52** was based on four incorrect hypotheses:

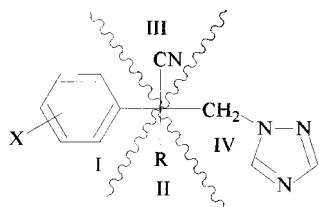
- 2,4-Dichlorosubstitution of the phenyl is best;
- no halogen on the phenyl ring is most cost-effective;
- greenhouse pot tests (inoculation within 24 hours of treatment) are good predictors of field performance; and
- as a consequence of results from a) to c), imidazoles are superior to triazoles.[4.231]

Further development showed however that:

- using foliar sprays, triazoles are ultimately superior to imidazoles;
- the imidazole ring is much more sensitive than triazole against UV light;
- 4-chlorophenyl emerges as optimal, in agreement with its occurrence in many other agrochemicals; and
- as a consequence of the longer residual activity and the efficacy, the triazoles are to be preferred.

A first optimal triazole compound **4.53**, RH-5781F, has been set aside when it became clear that efficacious dosing is uneconomical.[4.232]

The optimal successor compound, myclobutanil has been arrived at after an additional strategy as follows. Structure **4.53** has been formally dissected into four quadrants:[4.231, 4.232]



4.53

I, the X-substituted aryl ring;
 II, the hydrophobic side chain;
 III, the cyano group; and
 IV, the azolylmethyl group.

Structural activity profiles have been newly established against wheat powdery mildew, stem rust, and leaf rust.[4.232]

In group I, X has then been changed, holding R = n-butyl constant: 4-halogen, 4-C₆H₅, and 4-CN all improved activity over 4-H.

Modification of group II infers that non-C atoms in the chain, as well as chain branching at α'-C (i.e. i-propyl versus n-propyl) have a negative influence on activity. With X = 4-Cl held constant, II has been reinvestigated to arrive at n-butyl or n-pentyl as optimum for R¹. [4.232]

Synthetic efforts have been assisted by applying Hansch structure—activity techniques to 65 title compounds,[4.233] using inhibition data against *Piricularia oryzae*, *Drechslera sorokiniana* and, for sterol [¹⁴C] demethylation enzyme assay, *Saccharomyces cerevisiae*.[4.234] Thus, optimum chain length of R, and nature and position of X have been confirmed.

Conformational minima for rotation around bonds N1-Cβ and Cα-Cβ have been calculated and have resulted in a folded conformer (Fig. 4.2) of **4.54B**, myclobutanil [88671-89-0].[4.233, 4.234]

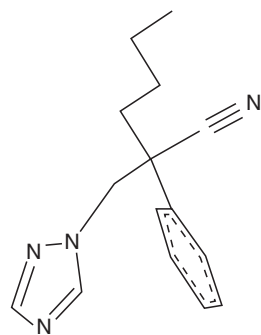
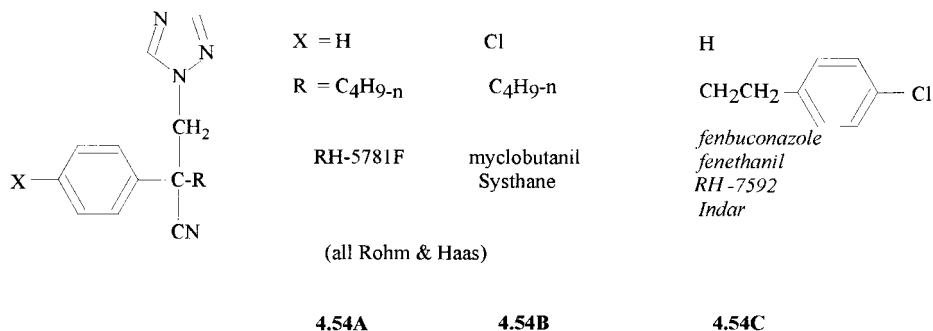


Fig. 4.2 Folded Conformer of myclobutanil; see p. 212 of ref. [4.233].

Thus, in the conformation preferred for antifungal activity, the agents phenyl ring is perpendicular to the supposed triazole—cytochrome P-450 bond. This conformation is possible for both **4.54B** and **4.54C**, but not for a substance with X² = Cl and R² = CN. Branching at the α'-position of R¹ disturbs the agents orienta-



tion towards the long planar surface of lanosterol and thus greatly lowers anti-fungal activity, although branching favors the folded form.[4.233]

In vitro activity of myclobutanil includes inhibition of *Ceratocystis ulmi*, *Penicillium digitatum*, *Aspergillus nidulans*, *Monilinia fructicola*, *Diaporthe phaseolum*, and *Rhizotonia solani*. [4.235] In greenhouse tests, myclobutanil displays high activity against *Erysiphe graminis* f. sp. *tritici*, *Puccinia tritici*, *Helminthosporium sativum*, and *Cercospora arachidicola*. [4.235]

Myclobutanil is recommended as broad-spectrum foliar fungicide for the control of *Uncinula necator* and *Guignardia bidwellii* on grapes, *Venturia inaequalis*, *Septorium* spp., *Cercospora* spp. and *Podosphaera leucotricha* on apple. [4.236, 4.237]

Myclobutanil is definitely lower in plant growth regulation activity compared with propiconazole. [4.236] Tolerances of myclobutanil and its metabolite have been established. [4.238]

The fit of myclobutanil to lanosterol has been improved by replacing butyl with 4-Cl-C₆H₄-CH₂CH₂- to arrive at fenbuconazole **4.54C**, [114369-43-6], with similar activity as the former, but improved inhibition of wheat leaf rust. [4.230, 4.231, 4.239]

This development followed the trend away from systemicity and selectivity against certain fungal groups towards lower MICs and higher broad-spectrum activity.

Fenbuconazole has been recommended for the control of *Septoria tritici*, *S. nodorum*, *Puccinia recondita*, *P. striiformis*, *Rhynchosporium secalis* in cereals, *Venturia inaequalis* on apples, *Monilinia* spp. on stone fruit, *Uncinula necator*, *Guignardia bidwellii*, *Botrytis cinerea* in grapes, and *Cercospora beticola* on sugar beet. [4.240, 4.241, 4.242]

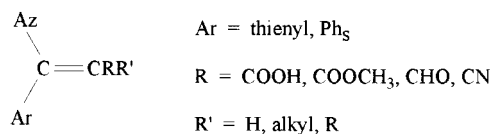
Metabolites of fenbuconazole have been prepared and biological properties studied. [4.243]

3-Substituted 1-(2-cyanoethyl)-1H-imidazolium salts are intermediates for a wide variety of 1-substituted 1H-imidazoles. [4.244]

4.12 1H-Azolylalkenyl carboxylic acids and their derivatives

4.12.1 1H-Azolylalkenyl carboxylic acids and esters

Title compounds **4.55** have been claimed as antimycotics and aromatase inhibitors for medical use, and as fungicides.[4.245, 4.246]

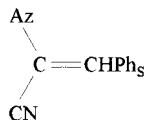


4.55

A paper describes the use of β -(1-imidazolyl)- α,β -unsaturated esters for the synthesis of 5-(1-imidazolyl-isoxazolidine-4-carboxylic acid esters).[4.247]

4.12.2 1H-Azol-1-yl-alkenyl nitriles

Title compounds **4.56** have been claimed as fungicides and aromatase inhibitors.[4.248]



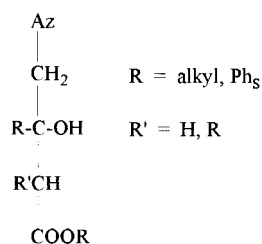
4.56

A paper reports the synthesis of 3-(1-imidazolyl)-methacrylo-nitriles, 2-methyl-3(1-imidazolyl)-acrylophenones and 2-methyl-3(1-imidazolyl)crotonates.[4.249]

4.13 1H-Azol-1-ylalkyl carboxylic acid derivatives with one or two further functional substituent(s) on the alkyl

4.13.1 1-(1H-Azoly-x-mono or x,y-di-hydroxyl)-alkyl carboxylic acid, their derivatives and thio analogs

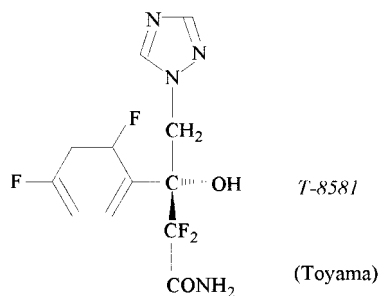
Title compounds **4.57** and their homologs have been reported as antimycotics which control experimental candidiasis, and fungicides which inhibit *Erysiphe graminis* on barley, and *Puccinia graminis* on wheat.[4.250, 4.251, 4.252, 4.253, 4.254, 4.255, 4.256, 4.257, 4.258]



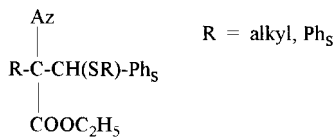
4.57

Some substances show plant growth regulation activity as well.[4.257]

Among these, compound **4.58**, T-8581 with superiority over itraconazole and fluconazole in the inhibition of *C. albicans*, shows high solubility in water (41.8 µg/ml, in contrast to fluconazole, 2.6 µg/ml) and thus promises to be useful for parenteral administration.[4.259]

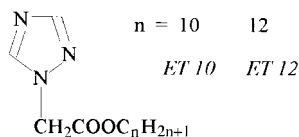


Another series includes thio analogs **4.59** and their metal salts as fungicides.[4.260, 4.261, 4.262, 4.263]

**4.59**

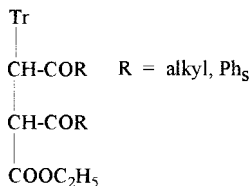
In most of the claims for **4.58** and **4.59**, ethers, esters and sulfonates of the hydroxyl and mercapto groups are included. These potential fungicides inhibit *Botrytis cinerea*, *Alternaria kikuchiana*, *Erysiphe polygoni*, *Rhizoctonia solani*, and *Helminthosporium oryzae*.

Further examples **4.60** represent compounds with activity against *Bacillus megaterium*, *C. albicans* and *Trichosporom cutaneum*. [4.264]

**4.60**

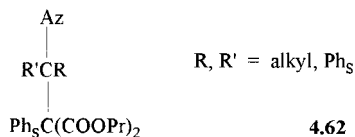
They quickly kill *Saccharomyces cerevisiae*. In their lysomotropic activity they come close to higher 1-alkylazoles such as 1-dodecyl-1,2,4-triazole, AT 12 (see section 2.1.4). [4.264]

Another series with one or two substituents is represented by **4.61** and controls powdery mildew. [4.265, 4.266]

**4.61**

A paper reports related bactericidal and fungicidal 3-aroyle-2-azolypropionic acids. [4.267]

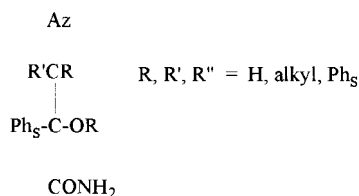
Yet another series **4.62** with fungicidal and plant growth activities includes a second carboxylic acid group. [4.268]

**4.62**

Some disclosures of this section also include carboxylic acid amides and nitriles.

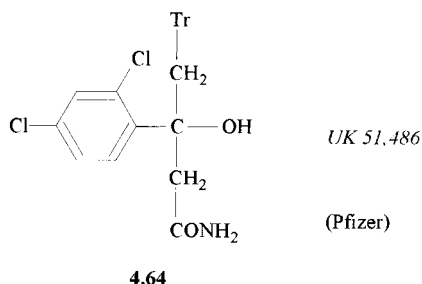
4.13.2 1H-Azolyalkyl carboxylic acids, esters, and amides, with one or two further substituents on the alkyl

Title compounds **4.63** have been claimed as antimycotics, which protect mice against the lethality of *Candida albicans* infection, and fungicides and also show plant growth control.[4.256, 4.269, 4.270, 4.271, 4.272]

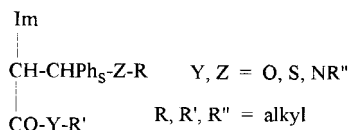


4.63

In these series, compound **4.64**, UK 51,486 has been discussed in a study to elucidate the problematic correlation between *in vitro* potency and *in vivo* efficacy of antimycotics. This agent resembles fluconazole more closely than ketoconazole in MIC values, pharmacokinetics, and efficacy in vaginal and systemic candidiasis models.[4.271, 4.273]



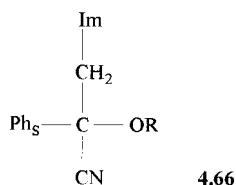
Other title compounds **4.65** have been claimed as fungicides which control *Sphaerotheca fuliginea*. [4.274]



4.65

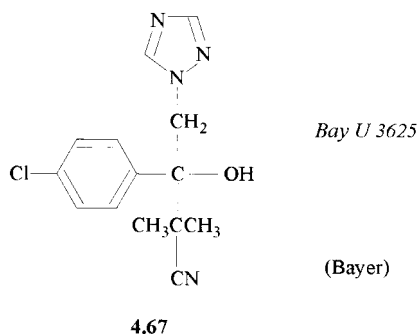
4.13.3 1H-Azolyalkyl nitriles with further reactive groups on the alkyl

Title compounds **4.66** represent antimycotics with high *in vivo* activity, after p.o. doses, against systemic *Candida albicans* and *Aspergillus fumigatus* infections in mice. Some samples (e. g. R = Pr) are comparable with fluconazole.[4.275, 4.276, 4.277, 4.278, 4.279, 4.280, 4.281, 4.282, 4.283, 4.284, 4.285]

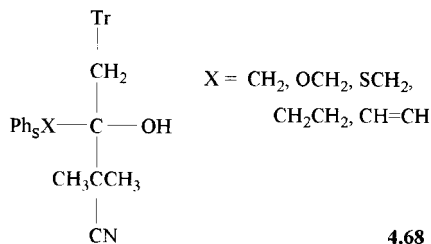


Fungicidal activity has been presented against *Helminthosporium* spp. and *Erysiphe graminis* on barley, *Puccinia graminis* on wheat, and *Botrytis cinerea* on peppers.

Within this series compound **4.67**, Bay U 3625 [131502-55-I] has been detected as one active metabolite of the oxime antimycotic Bay R3783 in rabbits (see section 5.7).[4.286]

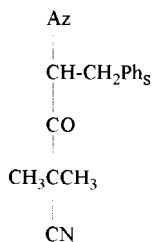


Another series **4.68**, also with high activity against systemic candidiasis in mice, carries two further substituents on the alkyl.[4.287]



Related series **4.69** carries a keto group as the additional substituent.[4.288]

These protect tomato plants from *Phytophthora infestans*.

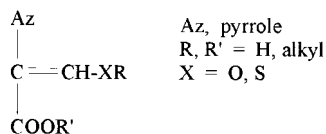


4.69

4.14 1H-Azolyalkenyl-carboxylic acid derivatives with further reactive groups on the alkyl

4.14.1 1H-Azolyalkenyl-carboxylic acid derivatives with O-substituents on alkenyl

Title compounds **4.70** have been claimed as fungicides.[4.289]

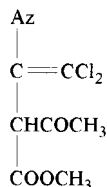


Az, pyrrole
 R, R' = H, alkyl
 X = O, S

4.70

They control *Venturia inaequalis* on apple, *Pyricularia oryzae* on rice, *Puccinia recondita* on wheat and also some show plant growth regulation.[4.289]

A series with an acyl group seems to lead mainly to plant growth-regulating agents, for example **4.71**.[4.290]

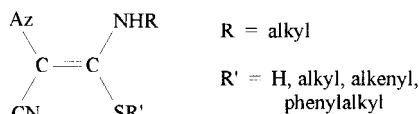


4.71

1H-Imidazol-1-yl-alkenyl-dicarboxylic methyl ester is formed by addition of dimethyl acetylene dicarboxylate to 1-acyl-imidazoles.[4.291]

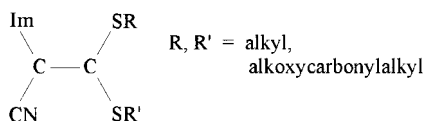
4.14.2 1-Azoly-alkenyl nitriles with N- and S-substituents on the alkenyl

Title compounds **4.72** which can also be considered as ketene S,N-acetals, have been claimed as fungicides.[4.292, 4.293, 4.294]



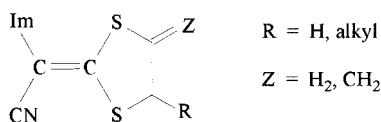
4.72

Other title compounds, ketene thioacetals **4.73** have been claimed as fungicides.[4.295, 4.296, 4.297]



4.73

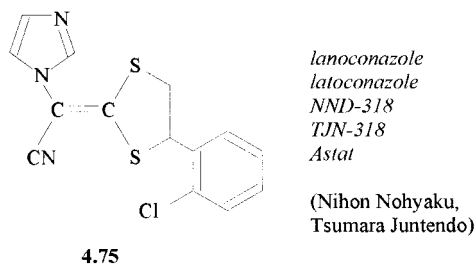
Cyclic thioacetals like **4.74** have been found to inhibit fungi.[4.298, 4.299, 4.300, 4.301, 4.302, 4.303, 4.304]



4.74

These inhibit *in vitro* *Trichophyton mentagrophytes*, control *Erysiphe graminis hordei* on barley, *Botrytis cinerea*, *Gibberella fujikuroi*, and *Fusarium oxysporum*.

From these series laniconazole, **4.75** [101530-10-3] has been marketed in the (E)-(±)-stereo form as a topical antimycotic with an additional wound-healing effect.[4.305, 4.306, 4.307, 4.308, 4.309]



4.75

Lanconazole is qualified as outstanding inhibitor of *Trichophyton* spp., *Aspergillus* spp., *Penicillium* spp., *Malassezia furfur* and *M. pachydermatis* and *Tinea versicolor* with superiority to bifonazole. It shows a high curative effect against tinea corporis and tinea pedis.[4.305] Secondary resistance is not easily developed by dermatophytes.[4.310] Recent clinical isolates and stock cultures of *Candida albicans* have the same sensitivity against lanconazole.[4.311]

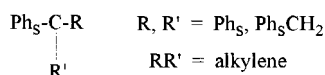
4.15 N-Acyl-imidazoles

N-Acyl-pyrazoles have been claimed as herbicides useful in rice fields.[4.312]

Title substances **4.76** have been disclosed and described in patents and papers as agricultural bactericides, fungicides, herbicides, plant growth regulators and intermediates.[4.313, 4.314, 4.315, 4.316, 4.317, 4.318, 4.319, 4.320]

Im

CO



4.76

These compounds control *Erysiphe graminis* on barley and *Botrytis cinerea* on cucumber.[4.321] In a structure—activity study against these fungi, substituents S = Cl, CH₃O and 3,4-Cl₂ have been found optimal.[4.319] Some of these products also have plant growth regulation activity.

The acyl group of the title compounds can include a α,β -C=C bond.[4.322, 4.323, 4.324]

1-[2-Naphthoxyacetyl]imidazoles have been prepared and screened for anti-microbial activity. [4.325]

Corresponding triazoles of this series are always less active than the imidazoles. As a rule, the (+)-isomer shows the higher antifungal activity. [4.319]

5 1H-Azoles or 1H-azol-1-ylalkyl compounds with a nitrogen functional group

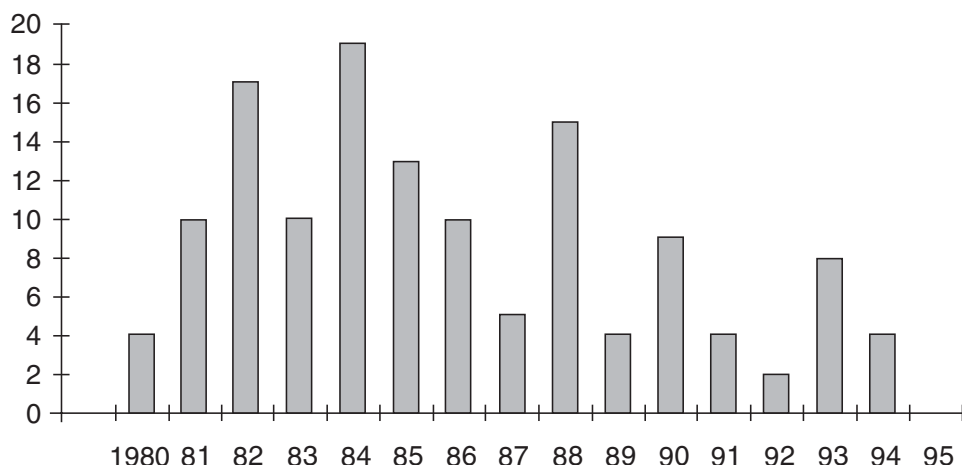


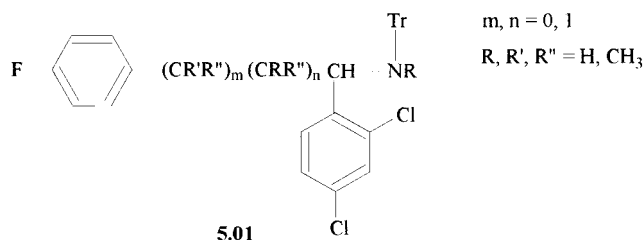
Fig. 5.1 Chronology of 134 patent applications of Chapter 5.

5.1 1-Amino-1H-azole derivatives

1-Amino- and 1-acetylamino-2-alkyl-4-phenyl-imidazoles and -triazoles inhibit *Staphylococcus aureus*, *Candida albicans* and *Erysiphe graminis*. [5.001, 5.002, 5.003, 5.004]

(For 1-Arylidenamino)-imidazoles, see section 5.8).

A large number of 1-(1,x-diphenylalkylamino)-1H-1,2,4-triazoles **5.01** have been investigated for structure—activity relations against *Venturia inaequalis* on apples, *Cercosporidium personatum* on peanuts, *Erysiphe graminis* and *Puccinia recondita* on wheat. [5.005]



The main fungicidal activity rests in the (R,S)-stereomer. Overall efficacy and antifungal spectrum of the optimal compounds is less well balanced than in the standard flusilazole.

1-(2,4-Dioxo-4-phenylbutyramide)-1,3,4-triazoles show bactericidal activity.[5.006]

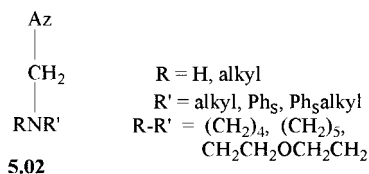
Related substances with $m = 1$, $R'' = OH$ display potent activity against *Candida albicans*. [5.007, 5.008]

5.2 1-(1H-Azol-1-yl)alkylamines and derivatives

5.2.1 1-(1H-Azol-1-yl)methylamines and derivatives

1-(3-Phenylpyrazol-1-yl)methyl-morpholines have been disclosed as fungicides which control *Botrytis cinerea* on cucumber plants.[5.009, 5.010]

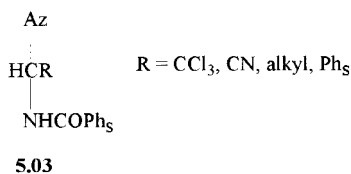
Title triazoles **5.02** have been claimed as bactericides, fungicides and algicides. They inhibit e.g. *Alternaria tenuis*, *Escherichia coli* and many algae spp.[5.011]



N-(Dimethylaminomethylene)-1,2,4-triazole oxalate controls *Puccinia recondita* f. sp. *tritici* on wheat. [5.012, 5.013]

1-[2-(Alkylthio)-6-benzothiazolylaminomethyl]-5-phenyl-1,2,3,4-tetrazoles show virucidal activity. [5.014]

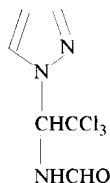
Benzamides **5.03** have been claimed as agricultural bactericides with activity against *Sphaerotheca fuliginea*, [5.015, 5.016], *Erysiphe graminis* on wheat, and *Uromyces phaseoli* on beans.[5.017, 5.018, 5.019]



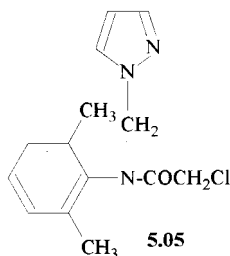
A paper covers general synthetic aspects.[5.020]

Pyrazolyl formamides like **5.04** control *Xanthomonas campestris* and *Pyricularia oryzae*. [5.021, 5.022, 5.023]

Further development resulted however in a new herbicide **5.05**, metazachlor [67129-08-2]. [5.024]



5.04

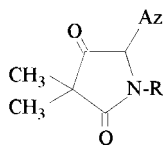


metazachlor
BAS 47 900H
Bulisan S

(BASF)

5.05

A cyclic analog **5.06** of the title series has been claimed as fungicide.[5.025]

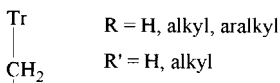


R = Ph₅

5.06

5.2.2 1-(1H-Azol-1-yl)ethyl-2-amines, their thio analogs and derivatives

Title compounds **5.07** have been claimed as antimycotics, with activity against *Candida* spp., *Trichophyton rubrum*, *T. mentagrophytes*, *Microsporum canis*, and *Epidermophyton floccosum*. [5.026, 5.027, 5.028, 5.029, 5.030]



R = H, alkyl, aralkyl

R' = H, alkyl

Ph₅CH-NRR'

5.07

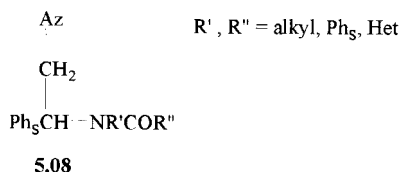
They include potential fungicides which protect wheat against *Erysiphe graminis*, cucumber plants against *Sphaerotheca fuliginea*, and control *Alternaria alternata*.

Substances **5.07** with R = H, R' = eicosapentaenoyl display cytoprotective activity and prevent the metastasis of cancer cells.[5.031, 5.032]

In some title series, the amino nitrogen is part of a piperazine ring.[5.033, 5.034] These substances have been disclosed as antimycotics with activity against Gram-positive and Gram-negative bacteria, yeasts, and filamentous dermatophytes including *Trichomonas vaginalis* with *in vitro* potency against blastomycetes surpassing miconazole.[5.035]

In other related title series of potential antimycotics, with R' representing phenylalkyl, the alkyl may be interrupted by one or two of O, S, SO or SO₂ groups.[5.036]

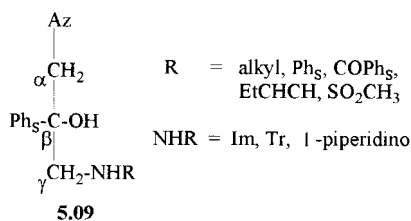
N-(Azol-1-yl)ethyl carboxamides **5.08** have been claimed as antimycotics and fungicides.[5.037, 5.038]



They have also been recommended for the treatment of steroid-dependent tumors.[5.039] Synthetic aspects have been covered in a paper.[5.040]

5.2.3 1-(1H-Azol-1-yl)alkylamines with a further substituent on the alkyl and their derivatives

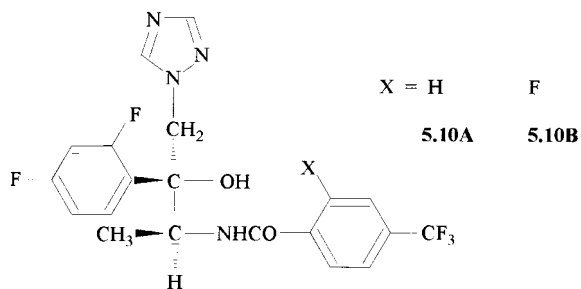
Most title compounds of the optimal form **5.09** which carry hydroxyl at C_α or C_β and amino at C_γ, C_δ..., have been claimed as antimycotics, showing protective action against a mouse systemic *Candida albicans* infection.[5.010, 5.041, 5.042, 5.043, 5.044, 5.045, 5.046, 5.047, 5.048, 5.049]



Some of these compounds are superior to fluconazole by a factor of 5 to 10.[5.050] The highest activity against systemic *Candida* infection of mice rests in the (2*R*,3*R*)-configuration.[5.051]

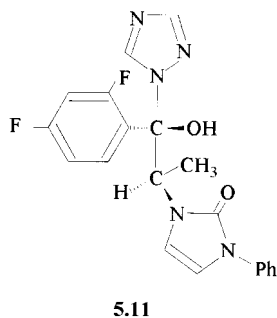
As fungicides, substances **5.10** inhibit *Puccinia recondita* on wheat, *Rhizoctonia solani* on rice and *Erysiphe graminis* on barley. Examples **5.10A** and **5.10B** appear particularly promising.

The (–)-stereomer of **5.10A** is superior to fluconazole and equivalent to Sch-42427 in the rat model of vaginal candidiasis.[5.050]

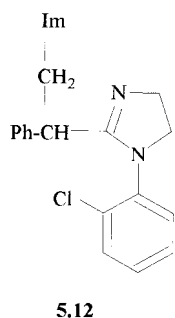


The amino nitrogen of the title compounds can also be part of a piperidine,[5.052, 5.053] a piperazine, [5.054, 5.055] or a morpholine ring.[5.056] High antimycotic activity against *Candida albicans* and fungicidal action against *Pyrenophora teres* on barley and *Uromyces appendiculatus* on bean has been demonstrated. Inhibition of tumor cells has also been detected.[5.053]

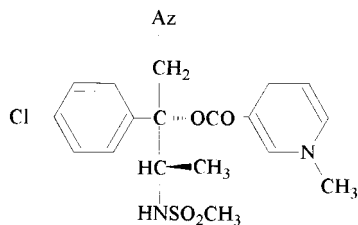
Compounds **5.11** and **5.12**, in which the amino group is part of a cyclic structure, represent potential antimycotics with high activity against mouse systemic *C. albicans* infection.[5.057, 5.058]



A series exemplified by **5.12** represents potential bactericides due to their inhibition of *Bacteroides fragilis*. [5.059]

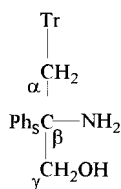


Esters **5.13** are considered antifungal prodrugs recommended for the treatment of cryptococcal meningitis accompanying AIDS.[5.060]



5.13

Series **5.14** of the title compounds, with hydroxyl at C $^{\alpha}$ and amino at C $^{\beta}$, shows antimycotic activity against *Candida* infection of mice.[5.061]

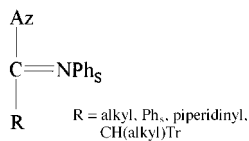


5.14

5.3 1-(1H-Azol-1-yl)-ketimines and -iminocarboxylic acid thiol esters

5.3.1 1-(1H-Azol-1-yl)ketimines

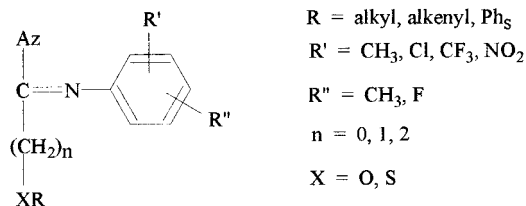
Title compounds **5.15** have been described in disclosures and papers as fungicides.[5.062, 5.063, 5.064]



5.15

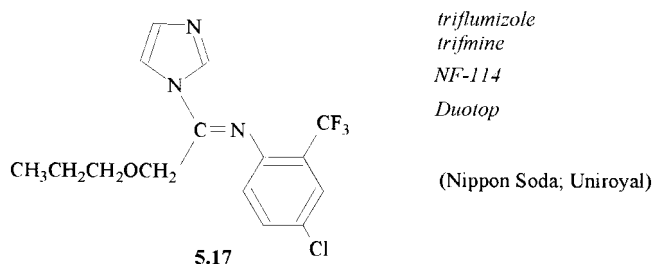
5.3.2 1H-Azol-1-yl-iminocarbonic and -carboxylic acid esters and their thio analogs

Title compounds **5.16** have been claimed as fungicides which control *Spaerotheca fuliginea* and *Pseudoperonospora cubensis* on cucumber, *Puccinia recondita*, *Helminthosporium oryzae*, *Erysiphe graminis* on barley, and *Fusarium moniliforme*. [5.066, 5.067, 5.068, 5.069, 5.070, 5.071, 5.072, 5.073, 5.074, 5.075]



5.16

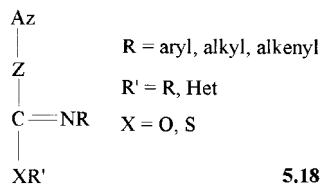
From these series, triflumizole **5.17**, [(*E*)-isomer, 99387-89-0; unstated stereochemistry, 68694-11-1] has been developed. [5.065, 5.076, 5.077]



Quantitative structure—activity correlations and molecular graphics have been studied. [5.078] This systemic fungicide with protective and curative action controls *Gymnosporangium*, *Venturia* spp. and powdery *Erysiphaceae* on pome fruit, *Helminthosporium*, *Tilletia* and *Ustilago* spp. on cereals, and *Fusarium*, *Fulvia* and *Monilinia* spp. [5.076, 5.079]

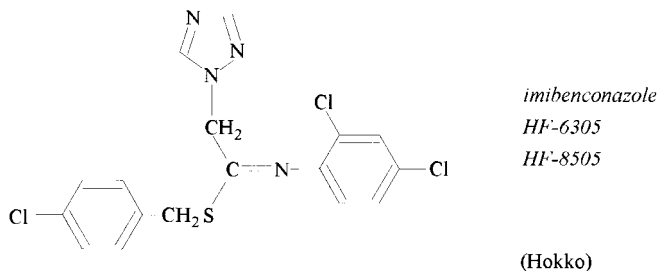
The tolerances of triflumizole have been established. [5.080]

Homologous title compounds **5.18** show activity against *Puccinia recondita*, *Sphaerotheca fuliginea* and *Rhizotonia solani*. [5.081, 5.082, 5.083, 5.084, 5.085] They can be stabilized by amines. [5.086]



Some of these compounds control *Valsa ceratosperma* on apple trees.[5.083] They inhibit *Coriulus versicolor*, *Tyromyces palustris* and *Serpula lacrymans* which recommends them for the protection of construction wood.[5.084]

In particular, imibenconazole **5.19**, [86598-92-7] has been selected for further trials.[5.087, 5.088, 5.092]



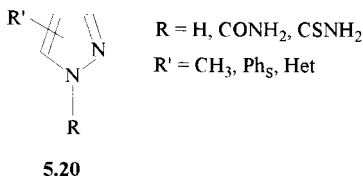
5.19

Stable aqueous suspensions and stabilized granular storage forms have been achieved.[5.089, 5.090, 5.091]

Imibenconazole controls ascomycetes, basidiomycetes and deuteromycetes on cereals, grapes, pome and stone fruit.[5.087] It acts as soil fungicide against *Rhizoctonia solani* on tomatoes. It shows excellent performance against *Venturia inaequalis*, *Podosphaera leucotricha* and *Gymnosporangium yamadae* on apple, *V. nashicola* and *G. asiaticum* on pears, *Ucinula necator* and *Elsinoe ampelina* on grapes, *Cladosporium carpophilum* on pears, *Puccinia recondita* and *Tilletia caries* on wheat, *Diplocarpon*, *P. horiana* and *P. zoysiae*. [5.088]

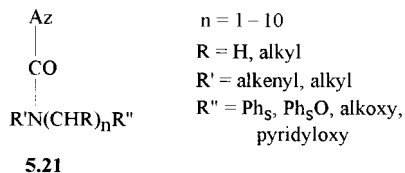
5.4 1-(1H-Azole) carboxamides and their thio analogs

Title compounds can be regarded as substituted ureas. The pyrazole example **5.20** shows bactericidal activity against *Staph.aureus*. [5.093]



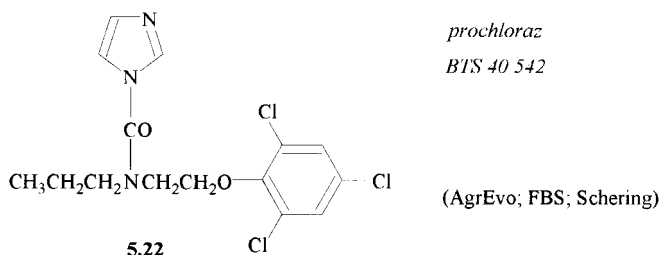
Antibacterial and antimycotic activity has been demonstrated of their neutral Cu, Co and Ni complexes.[5.094]

Tertiary amino groups are incorporated in general formula **5.21**. [5.095, 5.096, 5.097, 5.098, 5.099, 5.100, 5.101, 5.102, 5.103, 5.104, 5.105, 5.106, 5.107]



These substances control *Piricularia oryzae* and *Gibberella fujikuroi* on rice, *Erysiphe graminis* and *Puccinia recondita* on wheat, *Venturia inaequalis* on apple, *Sphaerotheca fuliginea* and *Pseudoperonospora cubensis* on cucumber plants and *Botrytis cinerea* on pepper plants.

From these series, prochloraz **5.22**, [67747-09-5] has been developed. [5.108, 5.109, 5.110, 5.111, 5.112]



Prochloraz is now a well-established protectant and eradicator fungicide against *Pseudocercospora herpotrichoides*, *Pyrenophora*, *Rhynchosporium*, *Septoria* spp., *Erysiphe*, *Alternaria*, *Botrytis*, *Pyrenopeziza* on oilseed rape, and *Sclerotinia*; *Colletotrichum* on coffee, *Pyricularia* on rice, and for seed treatment against *Cochliobolus*, *Fusarium*, and *Pyrenophora*. The drug controls the major fungal pathogens of the mushroom crop.[5.113]

Though prochloraz is readily absorbed by plant surfaces, it is not translocated over far distances. The metabolism of prochloraz in the rat has been elucidated.[5.114]

Salts of Sn, Zn and Co of prochloraz can also be used as fungicides.[5.115]

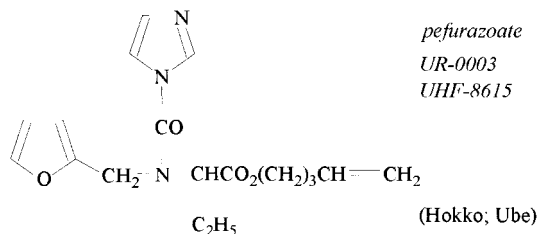
Five prochloraz analogs have been tested against cell-free extracts from *Penicillium italicum*. [5.116]

In other series **5.23** of the title compounds **5.21**, substituent R denotes a terminal carboxylic ester group CHCOOR' . [5.117, 5.118, 5.119, 5.120, 5.121] Further series of azolyl-1-carboxamides include furan-2-ylmethyl **5.24**, [5.122, 5.123, 5.124, 5.125, 5.126] 2,3-dihydrobenzofuran-2-ylmethyl, [5.127] and pyrimidin-2-yl as R' substituents. [5.128]

Some of these compounds control *Plasmopara viticola* on grape vine, [5.128] others inhibit *Valsa ceratosperma* on apple trees. [5.126]

From this body of disclosures, pefurazoate **5.23**, [101903-30-4] has been developed and microemulsion forms have been elucidated. [5.129, 5.130]

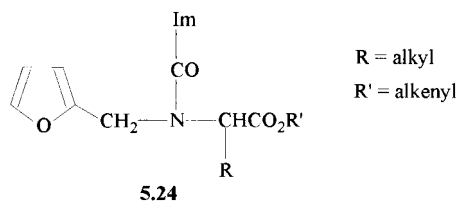
The main activity of pefurazoate against *Gibberella fujikuroi* rests in the (S)-stereomer. [5.131] The agent inhibits seedborne fungal diseases such as *Fusarium*



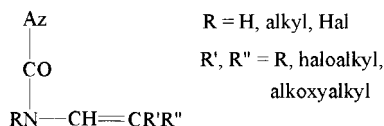
5.23

moniliforme, *Pyricularia oryzae* and *Cochliobolus miyabeanus* on rice, *Trichoderma viride* and moderately *Corynebacterium michiganense* on tomato.

Another group **5.24** of azolyl-1-carboxamides shows prominent activity against *Corioli* *versicolor*, *Tyromyces palustris* and *Serpula lacrymans*, which recommends it for the protection of wood.[5.132]

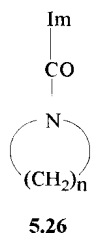


Azolylnylureas like **5.25** have been claimed as fungicides which inhibit *Erysiphe cichoracearum* on cucumber.[5.133]



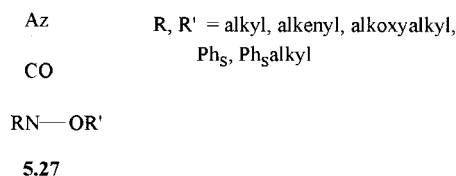
5.25

Cyclic analogs of the title compounds like **5.26** have been disclosed as fungicides which control *Botrytis cinerea* on beans and *Pyricularia oryzae* on rice seedlings.[5.134, 5.135, 5.136, 5.137, 5.145]



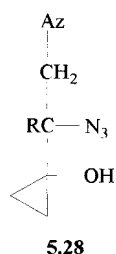
5.5 1-(1H-Azol-1-yl)carbamoyl-hydroxylamines

Hydroxylamines like **5.27** have been claimed for the control on *Botrytis cinerea* on pepper plants.[5.138]

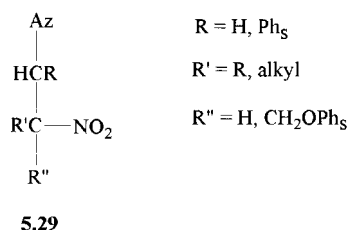


5.6 1-(1H-Azol-1-yl)-alkyl 2-azides, -nitro compounds and -hydroxylamines

Title compounds **5.28** control *Plasmopara viticola* on grapes.[5.139]



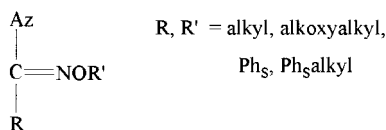
2-Nitroalkyl-azoles **5.29** have been claimed as antimicrobial finishing agents for laundry, and as fungicides which control *Erysiphe graminis* on wheat. [5.140, 5.141]



5.7 1H-(Azol-1-yl)-alkylaldehyde and ketone oximes, oxime derivatives, nitrones and hydrazones

5.7.1 1H-(Azol-1-yl)alkylketon-1-oximes

Title compounds **5.30** have been disclosed as fungicides which control e.g. *Piricularia oryzae*, *Sphaerotheca fuliginea* and *Botrytis cinerea*. [5.142, 5.143, 5.144]

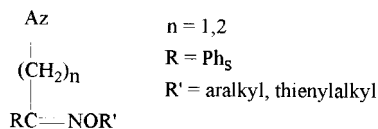


5.30

These series are generally also characterized by insecticidal activity.

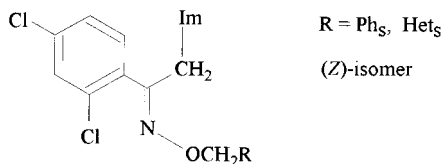
5.7.2 1H-(Azol-1-yl)alkylketon-2-oximes

Title compounds **5.31** have been claimed as bactericides which inhibit *Staph. aureus*, antimycotics against *Candida albicans*, and fungicides which control *Podosphaera leucotricha* on apple seedlings, *Cercospora* spp., and *Erysiphe graminis* on wheat. [5.146, 5.147, 5.148, 5.149, 5.150, 5.151, 5.152, 5.153, 5.154]



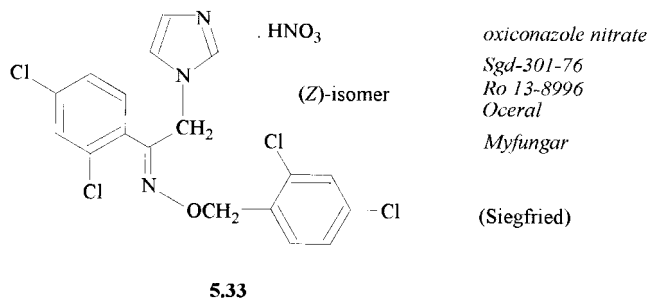
5.31

Some papers report on variation of R by 5-chlorothieryl-2-methyl and by x-halogen-(benzo[b]thienyl-2- or 3-methyl- yielding substances **5.32** which inhibit *in vitro* *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus* spp. [5.155, 5.156]



5.32

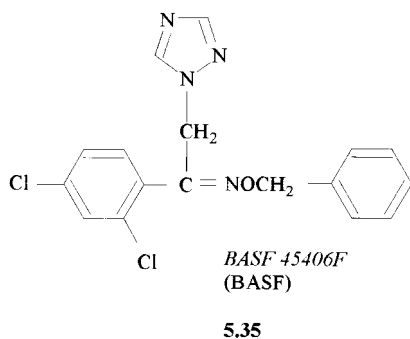
Out of these series, oxiconazole **5.33**, [base, 64211-45-6; nitrate 64211-46-7] has been developed as a broad-spectrum antimycotic with fungicidal and fungistatic action.[5.157]



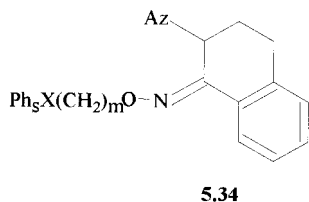
Physicochemical properties of oxiconazole nitrate,[5.158] pharmacology, pharmacokinetics, permeation, efficacy, safety and adverse effects have been reviewed recently.[5.159, 5.160, 5.161, 5.162]

Oxiconazole formulations as cream, solution or powder show good efficacy in the local treatment of fungal infections of the skin and are available for self-medication.[5.163, 5.164, 5.165] In tablet form oxiconazole is very useful against vaginal mycoses.[5.166] Favorable clinical experience has been reported in the treatment of mycotic keratitis caused by *Aspergillus terreus* in a corneal ulcer.[5.167] Non-irritating fungicidal eye drops have been claimed.[5.168]

A closely related triazole analog BAS 45406F, **5.35** [77562-07-3] has been suspended from further development.[5.171]

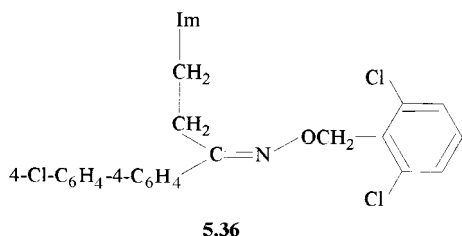


Cyclic analogs of the title compounds are represented by series **5.34**.[5.169, 5.170]



5.7.3 1-(1H-Azol-1-yl)alkylketon-3 oximes

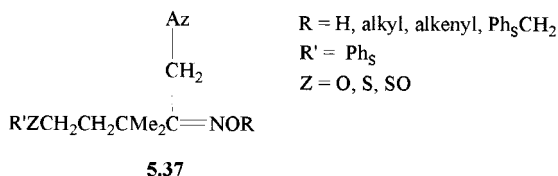
Title compounds **5.36** have been disclosed as fungicides and plant growth regulators.[5.172]



5.7.4 1-(1H-Azol-1-yl)alkane-aldehyde- or -keton- oximes with further substituents on the alkyl

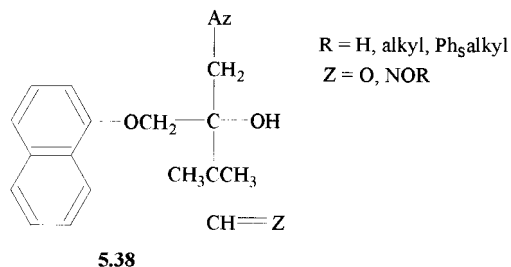
4-Arylthio-2-oximino-1-(1H-azole) ethers have been claimed as fungicides.[5.173] 5-Phenoxy-2-oximino-1-(1H-azole) ethers **5.37** control *Cochliobolus sativus* on barley.[5.174]

2-Hydroxy-3-phenoximino-1-(1H-azol-1-yl)alkanes show superior activity against *Puccinia recondita* on wheat.[5.175] 2-Hydroxy-4-oximino-1-(1H-azol-1-yl)alkanes **5.38** have been disclosed as antimycotics, with high activity against *C.*



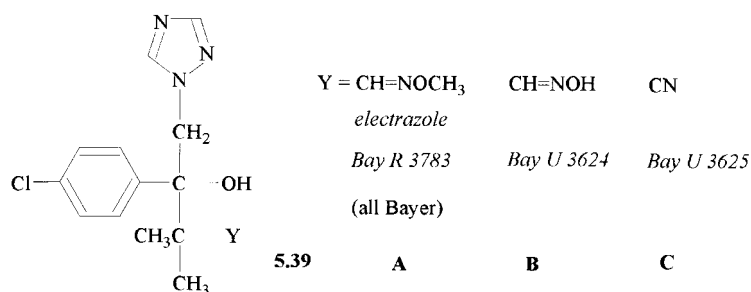
albicans, and as fungicides.[5.176, 5.177, 5.178, 5.179]

A methoxymethyl-oxim ether **5.40B** is superior to fluconazole after p.o. administration to infected mice by a factor of ca. 12 against *Candida albicans* and of >3.3 against *Aspergillus fumigatus*.[5.179]



A new potential oral antimycotic, eletrazole **5.39A**, [104142-35-0] is comparable with or slightly superior to fluconazole against superficial and systemic candidiasis, meningocerebral cryptococcus, *Coccidioides immitis*, and pulmonary aspergillosis. [5.180, 5.181, 5.182]

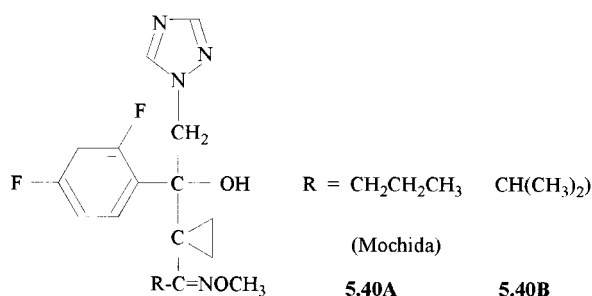
Eletrazole surpasses itraconazole, fluconazole and ketoconazole in activity against *Blastomyces dermatidis* and is similar to itraconazole against *Histoplasma capsulatum*. [5.180, 5.181] Bay R 3783 surprises by longstanding antifungal activity



in the *Candida albicans* infection model of the mouse, though the plasma half-life is only 2 hours. [5.182, 5.183, 5.184]

In fact, eletrazole is biotransformed in the mouse, rat, rabbit, cat, dog, ape and man into the active metabolites **5.39B**, Bay U 3624 and **5.39C**, Bay U 3625. The latter shows a half-life of 9 hours (mouse) and 48 hours (rabbit) and represents the prominent carrier of the antimycotic action. [5.183] However, in spite of this promising potential, Bay-R 3783 had to be discontinued from active development due to hepatic toxicity, possibly caused by metabolism of the oxime to the nitrile. [5.182, 5.185, 5.186]

Cyclic analogs of eletrazole, not metabolized to nitriles, are represented by **5.40A** and **5.40B**. [5.186]

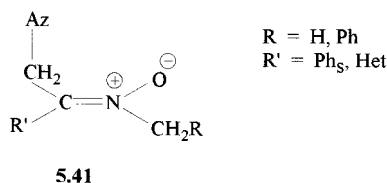


These appear superior to fluconazole and itraconazole against systemic aspergillosis in mice and vaginal candidiasis in immunosuppressed mice.

Other title oximes with a keto group or a second ketoxime group as the additional substituent have been disclosed as fungicides. [5.187, 5.188] The synthesis of oximes with additional carboxylic ester groups has been investigated. [5.189, 5.190]

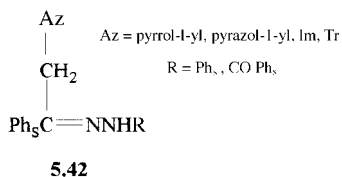
5.7.5 1-(1*H*-Azol-1-yl)methyl nitrones

Title compounds **5.41** are starting materials for antifungal isoxazolines (see section 6.3).[5.191]



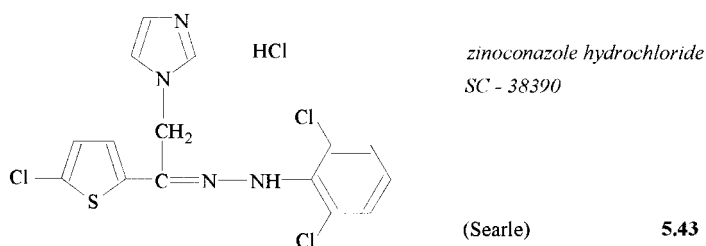
5.7.6 1-(1*H*-Azol-1-yl)alkylketon hydrazones and semicarbazones

Title compounds **5.42** with Az = pyrrol-1-yl, have been disclosed as antimycotics with *in vitro* inhibition of a large group of *Candida* spp.[5.192]



1-Pyrazole derivatives of the title compounds **5.42** with R = CONHPh_s and (*Z*)-stereochemistry give complete control of *Spodoptera litura*. [5.198]

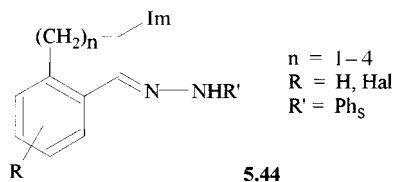
Their imidazole derivatives show antifungal activity superior to that of clotrimazole.[5.193] A thienyl analog zinoconazole **5.43**, [base, 84697-21-2; hydrochloride, 80168-44-1] has been selected as an antimycotic.[5.194]



The antifungal activities of the (*E*)- and (*Z*)-stereoisomers are quite similar.[5.195, 5.196] Control of the *Candida albicans* infection of the mouse after oral doses surpasses that of ketoconazole.

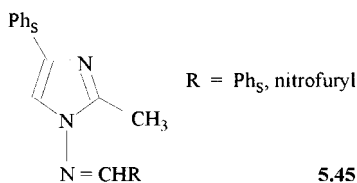
The 1,2,4-triazole analog of zinoconazole shows antimycotic activity similar to that of miconazole.[5.197]

Cyclic analogs **5.44** inhibit anaerobic bacteria such as *Propionibacterium acnes*. [5.199, 5.200]

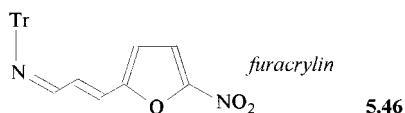


5.8 1-Arylidenamino-(1H-azoles)

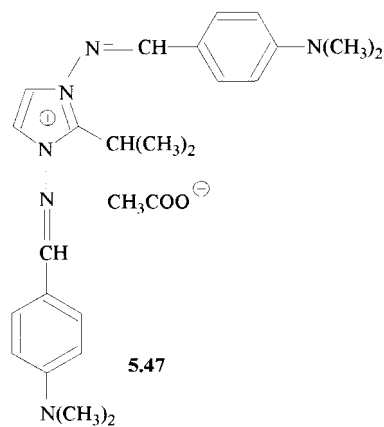
Title imidazoles **5.45** inhibit *Staphylococcus aureus* and *Candida albicans*. [5.001, 5.002]



A vinylogous analog **5.46**, [10048-74-5] is presented by the bactericide furacrylin. [5.201]



1,3-Disubstituted imidazolium salts **5.47** have been disclosed as potential bactericides, antimycotics and protozoacides.[5.202, 5.203, 5.204]



This agent controls *Litomosoides carienii* infection of *Sigmodon hispidus*.

6 x-(1H-Azol-1-yl)methyl-isoxazolidines, oxazolines, -oxazolidines, -oxetanes, 1,3-dioxolanes, -morpholines, 1,3-dioxanes, -tetrahydrofurans, their thioderivatives and homologs

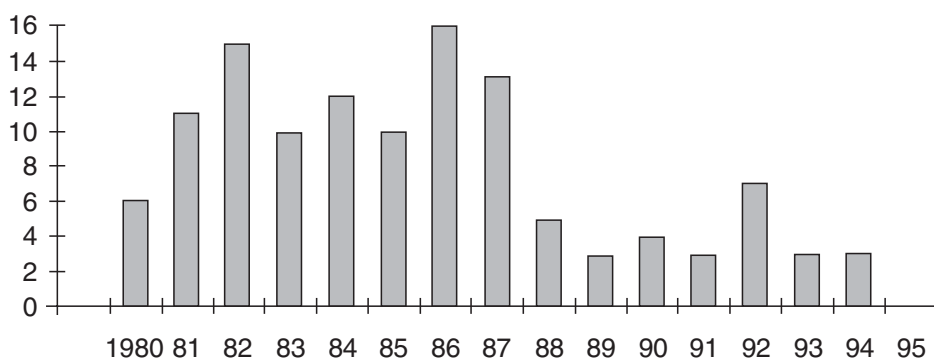


Fig. 6.1 Chronology of 121 patent applications of Chapter 6.

6.1 x-(1H-Azol-1-yl)methyl-isoxazolidines, isoxazolines, -oxazolidines, 1,3-dioxolanes, -1,3-dioxanes, morpholines, -tetrahydrofurans, their thioanalogs and homologs, without further basic nitrogen substituents

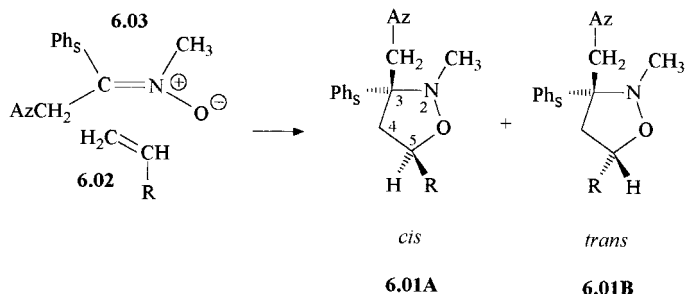
6.1.1 2-(1H-Azol-1-yl)methyl-thiazolidines

Title thiazolidines protect rice against *Rhizoctonia solani* and *Cercospora arachidicola* on peanut plants.[6.001, 6.002]

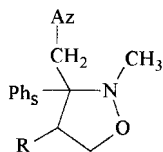
6.1.2 *x*-(1*H*-Azol-1-yl)methyl-isoxazolidines and isoxazolines

6.1.2.1 3-(1*H*-Azol-1-yl)methyl-isoxazolidines

Title compounds have been obtained as *cis*- and *trans*-isomers **6.01A** and **6.01B** by regioselective 1,3-dipolar cycloaddition reaction of monosubstituted, electron-rich (i.e. R = Ph) olefins **6.02** to azoly-nitrones **6.03** (see section 5.7.5).[6.003, 6.004]



These 5-substituted isoxazolidines show the desired antifungal activity. Highly electron-deficient olefins (i.e. R = NO₂) result exclusively in 4-substituted products **6.04**.



6.04

In an outstanding research program of medicinal chemistry, 14 patent applications on compounds **6.01** have been filed, within only 1½ years, [6.003, 6.005, 6.006, 6.007, 6.008, 6.009, 6.010, 6.011, 6.012, 6.013, 6.014, 6.015, 6.016, 6.017 and 33 papers have been published,[6.004, 6.018, 6.019, 6.020, 6.021, 6.022, 6.023, 6.024, 6.025, 6.026, 6.027, 6.028, 6.029, 6.030, 6.031, 6.032, 6.033, 6.034, 6.035, 6.036, 6.037, 6.038, 6.039, 6.040, 6.041, 6.042, 6.043, 6.044, 6.045, 6.046, 6.047, 6.048, 6.049] all by the research group of Pennwalt.

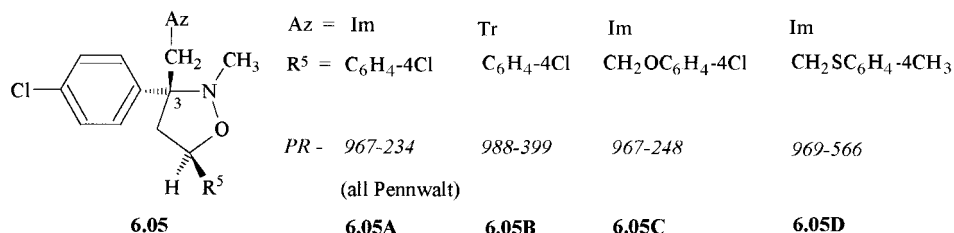
In the group of *cis*-imidazolymethyl-derivatives, optimization of R for *in vitro* activities against *Trichophyton rubrum*, *Candida albicans* and especially *Aspergillus fumigatus* with ketoconazole as standard, substituents n-C₆H₁₃, 4-CH₃C₆H₄SCH₂-, [6.048] 4-ClC₆H₄-, 4-ClC₆H₄OCH₂-, [6.004] and in one case also *trans*-CH=CHC₆H₅ [6.030] have been found optimal. Of aromatic halogen, 2-Cl and 2,6-Cl₂ substitution result in similar activity than 4-Cl.

Further, substituent Ph_s includes 4F-C₆H₄-, 2-thienyl, [6.043] 2-furanyl, [6.004, 6.049] and in one case 2-naphthyl all with interesting antifungal activity.[6.030]

From these series, *cis*-3-(4-chlorophenyl-5-hexyl-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-isoxazolidine and 3-(1*H*-imidazol-1-ylmethyl-*N*-methyl-3-(2-naphthyl)-5-2-*trans*-phenylethenyl-isoxazolidine have been studied further but were then discontinued.[6.050, 6.052]

In *cis/trans* couples of imidazolyl title derivatives, the *trans*-forms **6.01B** generally show weaker *in vitro* inhibition of *T. rubrum*, and much weaker inhibition of *A. fumigatus* than the *cis*-isomers **6.01A**.[6.004]

The total work cited above has produced three eminent imidazole *cis*-compounds **6.05A**, PR 967-234 [113614-50-9]; **6.05C**, PR 967-248 [114372-38-2]; **6.05D**, PR 969-566 [113944-05-1]; and **6.05B**, PR 988-399 [114606-88-1], which is the 1,2,4-triazole analog of **6.05A**, also in *cis*-configuration.[6.004, 6.027]

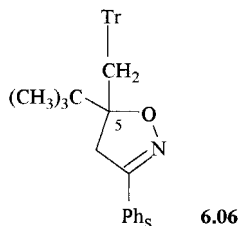


Their antifungal activity *in vitro* against *Candida*, *Aspergillus* and dermatophytes ranks **6.05A** ≥ **C** ≥ ketoconazole ≫ **B** (> indicates that activity is better than); however, against two strains of *C. albicans* causing rat candidial vaginitis, the ranking is ketoconazole > **B** > **D** > **C** > **A**, which contrasts to the *in vivo* efficacy of ketoconazole > **D** ≫ **A**.[6.042] While 1,2,4-triazole derivatives have been generally inferior to their imidazole analogs, the *in vivo* efficacy of **B** is superior to its imidazole analog **A**. In using three species of *C. albicans*, compound **B** approaches ketoconazole on the 7th and 8th day after infection; it has achieved complete cure of rat vaginal candidiasis just 1 to 2 days later than ketoconazole.[6.004] In the mouse model of disseminated candidiasis, **B** is even superior to the standard.

Regarding safety (hormonal, central nerve system, and cardiovascular effects), isoxazolidines **D** and **B** rank closely with ketoconazole, while **A** and **C** fall off.[6.004, 6.042] Thus, **B** has been selected for further development.

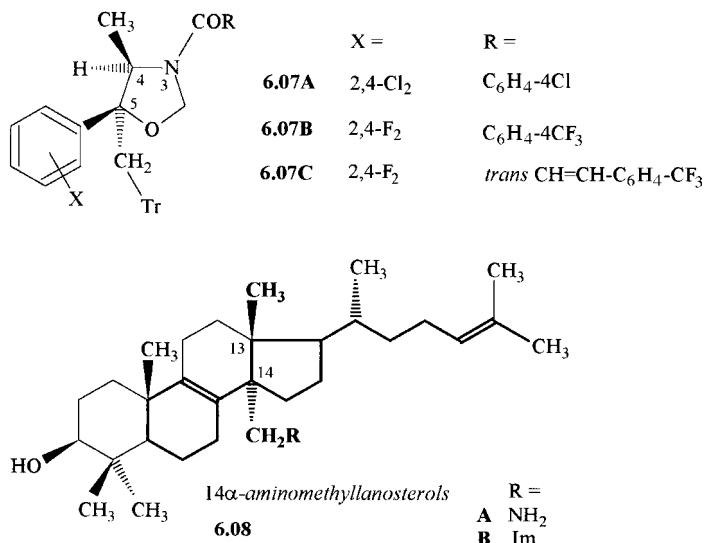
6.1.2.2 5-(1*H*-1,2,4-Triazol-1-yl)methyl-isoxazolidines

Title compounds like **6.06** have been claimed as fungicides which control e.g. mildew on cucumber, and as plant growth regulators.[6.052]



6.1.3 5-(1*H*-Azol-1-yl)methyl-oxazolidines

Title compounds **6.07** have been designed in order to mimic the skeleton in the model 14-imidazolylmethyl lanosterol **6.08B**. [6.053, 6.054, 6.055, 6.056]



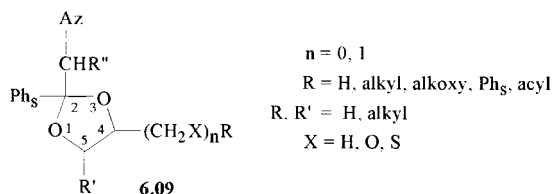
The best antifungal compounds include **6.07A** as (+)-(4*R**,5*R**)-stereomer, **6.07B** which is active as the (–)-stereomer, [6.057] and **6.07C**. [6.058] Crystal structures of the two diastereomers have been determined. [6.058] Although *in vitro* studies have shown low activity against *C. albicans*, *in vivo* use against systemic candidiasis in mice has demonstrated compound **6.07A** as the optimum. The surfaces of **6.07B** or **6.07C** are envisioned to dock to the antifungal lanosterols **6.08**. 5β-Aromatic ring and the oxazolidine ring of **6.07** superimpose to rings B and D of **6.08**, as emphasized in bold lines in the drawing of the latter. [6.053, 6.055] This suggests that the 14-β-methyl plays an important role in the antifungal activity. [6.058]

6.1.4 2- and 4-(1*H*-Azol-1-yl)methyl-1,3-dioxolanes

6.1.4.1 2-(1*H*-Azol-1-yl)methyl-4-H-, or 4-alkyl- or 4-heterocycl-1,3-dioxolanes

Title substances **6.09** which can be regarded as cyclic ketals, have been disclosed as antimycotics and fungicides, [6.059, 6.060, 6.061, 6.062, 6.063, 6.064] and described in papers (compare also section 6.1.7.1). [6.065, 6.066, 6.067]

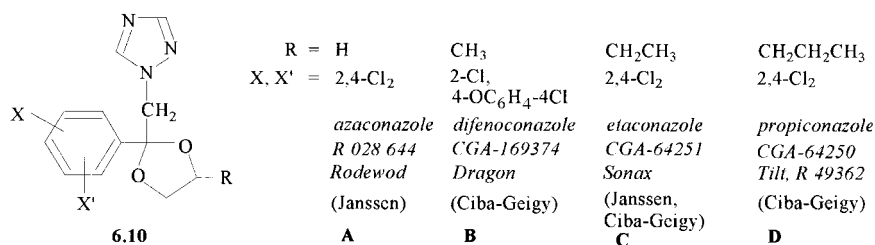
2-Bromomethyl-1,3-dioxolanes have been claimed as precursors. [6.068]



Title compounds inhibit *Staphylococcus aureus* and *Epidermophyton floccosum*, [6.063] and control *Helminthosporium gramineum* on wheat grains, *Puccinia graminis* on wheat, *Drechslera graminea* on barley, *Pyricularia oryzae* and *Valsa mali*. Some also show plant growth inhibition.

From these series, azaconazole, difenoconazole, etaconazole and propiconazole have been developed.

Azaconazole **6.10A** [60207-31-0] is particularly useful in the control of wood-destroying and sapstain fungi, such as *C. puteana*, *P. placenta*, *Gl. trabeum*, *C. versicolor* and *A. pullulans*, as a disinfectant for mushroom cultivation and fruit storage boxes, [6.066, 6.069] and for wood protection in general. [6.070]



It has been proposed for wound-healing preparations for trees. [6.069, 6.071, 6.072, 6.073]

Difenoconazole **6.10B** [119446-68-3] represents a systemic fungicide with preventive and curative action against *Alternaria* on potatoes and tomatoes, *Septoria*, *Cercospora* on sugar beet leaves, *Cercosporidium*, *Ascochyta*, *Ramularia*, *Venturia*, *Guignardia*, *Phoma*, *Colletotrichum* and some soilborne pathogens of crops and fruit. [6.073, 6.075, 6.076, 6.077] The drug can be assayed in vegetable tissue by GC. [6.078]

Etaconazole **6.10C** [60207-93-3], an isomeric mixture, seems to be superseded now. [6.079] The variation of the 4-substituent has been investigated systematically. [6.080, 6.081] A QSAR study is discussed under propiconazole (see below). All four stereoisomers of etaconazole have been prepared. [6.081] The main activity against *Cercospora arachidicola* infection on peanut and *Puccinia graminis* on wheat is located in the (2S,4R)-stereomer. [6.080, 6.081] Etaconazole has also been recommended as a wood preservative. [6.082]

Propiconazole **6.10D** [60207-90-1] represents a systemic, preventive and curative fungicide. [6.083, 6.084] It inhibits Ascomycetes, Basidiomycetes, Deuteromycetes, and controls *Rhynchosporium* on barley, *Septoria tritici* and *Puccinia recondita* on wheat, *Phymatotrichum omnivorum* on cotton and *Rhizotonia solani* on

rice.[6.085, 6.086, 6.087] It is also recommended for wood protection, as azaconazole (see above).[6.070]

All four stereoisomers of propiconazole have been prepared.[6.081, 6.088] The (2*R*,4*S*)-form shows better control of *Helminthosporium gramineum* on barley than the racemate.[6.088] ¹⁴C-Labeled propiconazole stereoisomers have been synthesized.[6.089, 6.090] Tolerances have been established for propiconazole and its metabolites.[6.091]

QSAR studies have been completed on etaconazole-and propiconazole-related compounds in respect to the influence on ergosterol biosynthesis of *Ustilago maydis*, the control of *Puccinia graminis* on wheat, *Cercospora arachidicola* on groundnut plants, and *Erysiphe graminis* on barley.[6.080]

Cis-stereomers of the propiconazole family show higher fungicidal activities than the racemates. Optimal fungicidal activity is correlated to a log *P* between 3 and 4. The size parameters of the para-substituent of the 3-phenyl, and that of the dioxolane substituents enter with a negative coefficient into the regression. The Hammett constant σ , with a value of about 1.5 corresponds to the sum of the 2-Cl- and 4-Cl-values for the best compound, but otherwise seems to have no significant influence.

Both 2*S*-enantiomers of etaconazole and propiconazole carry the highest antifungal activity, and there is practically no difference between 2*S*,4*S*- and 2*S*,4*R*-forms. Racemic propiconazole, e.g. in the commercial product Tilt, presently appears as the most active fungicide of the dioxolane- and dioxane-triazoles of section 6.1.

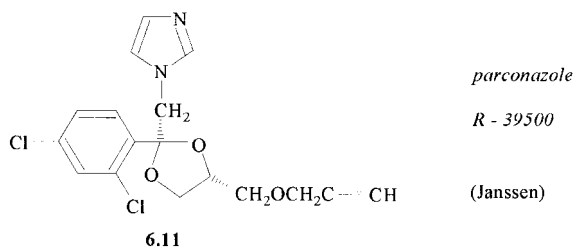
Propiconazole improves the biosynthesis of gliotoxin and glyovirin by *Gliocladium virens* cultures due to the control of phytotoxin viridiol.[6.092]

2,4-Bis(1*H*-azol-1-yl)methyl-2-phenyl-1,3-dioxolanes show bactericidal activity.[6.093]

6.1.4.2 2-(1*H*-Azol-1-yl)methyl-4-hydroxymethyl-1,3-dioxolane derivatives, homologs and thio analogs

Stereoisomers of 2-[ω-(2-1*H*-imidazol-1-ylalkyl)-(1,3-dioxolan-4-yl- and 1,3-oxathiolan-5-yl)methanols have been prepared.[6.094]

Parconazole **6.11**, [61400-59-7; hydrochloride 62973-77-7] has been developed as a broad-spectrum antifungal also with activity against Gram-negative bacteria.[6.095]

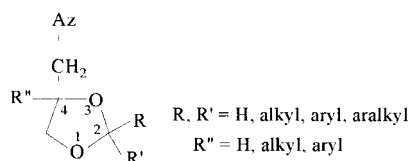


Studies on the molecular basis of its antimicrobial action have appeared, e.g. [6.096] and an improved powder has been formulated.[6.097]

6.1.4.3 4-(1*H*-Azol-1-yl)methyl-2-*H*, -2-alkyl- or 2-alkyloxy-1,3-dioxolane derivatives

4-Heterocyclylmethyl-1,3-dioxolanes have been claimed as bactericides and fungicides for plant protection.[6.098]

4-(1*H*-Azol-1-yl)-2-alkyl or 2-alkoxy-1,3-dioxolanes **6.12** have been disclosed as fungicides.[6.099, 6.100, 6.101, 6.102]

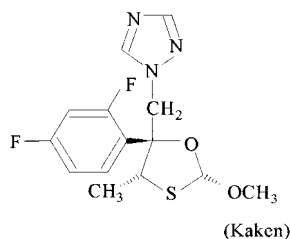


6.12

These substances control *Venturia inaequalis*, *Puccinia recondita* on wheat, and *Erysiphe graminis* on barley.

6.1.4.4 4-(1*H*-Azol-1-yl)methyl-2-hydroxy-oxathiolane

Compound **6.13** displays higher efficacy than fluconazole against candidiasis of immunosuppressed mice.[6.103]

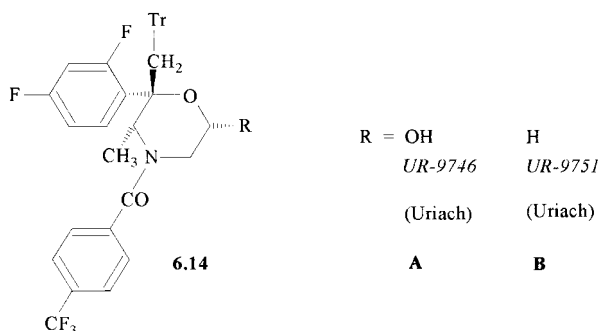


6.13

4-(1*H*-Azol-1-yl)methyl-1,3-dioxolanes, -1,3-dioxolan-2-ones and -1,3,2-dioxathialone-2-oxides have been studied in connection with azolypropanolones (see section 4.5.2) Interesting oral efficacy against murine candidiasis has been reported.[4.155]

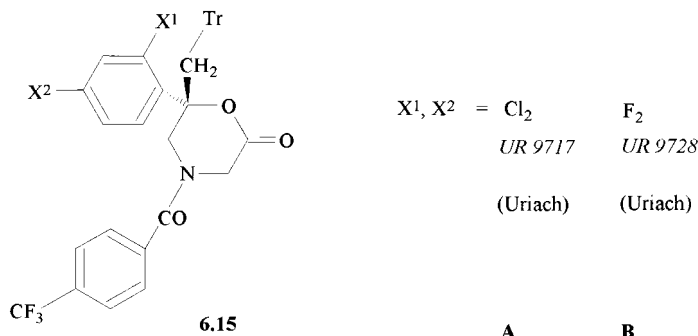
6.1.5 6-(1*H*-Azol-1-yl)methyl-4-benzoyl- morpholines and -morpholin-2-ones

Compounds **6.14A** and **6.14B**, both with eminent fungicidal activity as (–)-(5*R*,6*R*) stereoisomers, have been developed using stereochemical analogy with compound **6.07B**, and with stereochemically related piperidines.[6.057, 6.103]



Efficacy against the vaginal infection of the rat by *Candida albicans*, murine coccidiomycosis, histoplasmosis and cryptococcosis has demonstrated superiority of these compounds over fluconazole and itraconazole. However, **6.14** substances lack pronounced activity against murine aspergillosis. [6.057, 6.103]

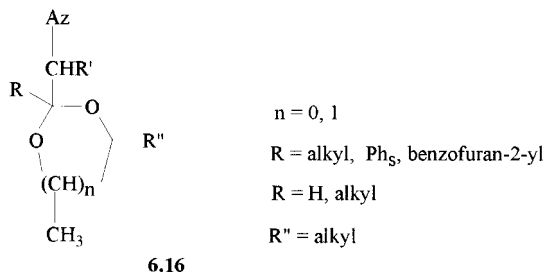
Of two morpholin-2-one analogs **6.15A** and **B**, UR-9728—in spite of little *in vitro* antifungal activity—has demonstrated higher efficacy against experimental systemic candidiasis and *C. cryptoformans* infection than itraconazole, and similar efficacy than Sch 42427 (see section 3.11.4). [6.104]



They also have shown superiority to fluconazole against *Cryptococcus* infection. Even so, investigation on both substances had to be discontinued.[6.105, 6.106]

6.1.6 2-(1H-Azol-1-yl)methyl-1,3-dioxacycloalkanes and derivatives

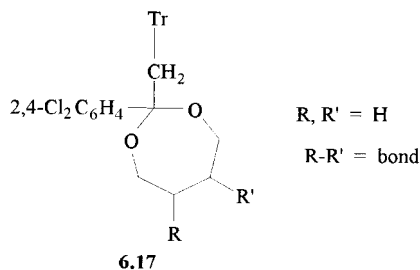
Claims for title 1,3-dioxacycloalkanes may also include 1,3-dioxolanes **6.16**. [6.061, 6.107, 6.108, 6.109, 6.110, 6.111, 6.112, 6.113, 6.114]



Structure—activity correlations have been studied for 2-(1H-1,2,4-triazol-1-yl)methyl-2-subst. phenyl-5-mono- or -disubst. 1,3-dioxanes. [6.081]

Members of these series have been demonstrated as potential antimycotics which inhibit *Candida*, *Epidermophyton*, *Aspergillus*, *Trichophyton*, *Microsporon* and *Penicillium*. As potential fungicides they control e.g. *Puccinia graminis* on wheat, *Botrytis cinerea* on beans, *Pyricularia oryzae* on rice and protect wood from fungal attack. [6.115]

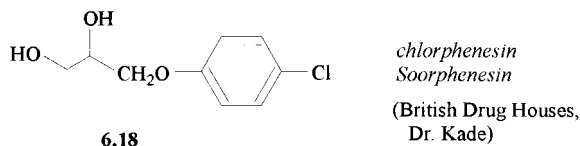
Dioxepins **6.17** have been claimed as fungicides. [6.116]



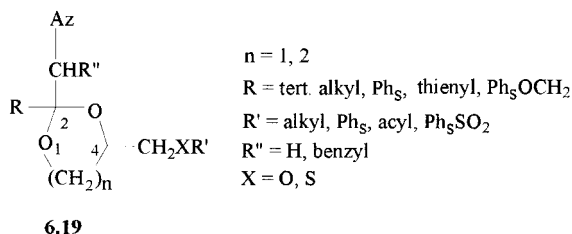
6.1.7 x-[1-(1H-Azol-1-yl)-y-(hydroxy and/or keto)]alkyl 1,3-dioxacycloalkanes and derivatives

6.1.7.1 2-(1H-Azol-1-yl)alkyl-4-hydroxyalkyl-1,3-dioxolanes

Since phenylalkyl substituents at C4 of 1,3-dioxolanes have been found interesting, this substituent has been further modified to $-\text{CH}_2\text{OPh}_s$, recalling the structure of chlorphenesin **6.18**, a topical antifungal agent discovered 20 years before the azoles. [6.117]

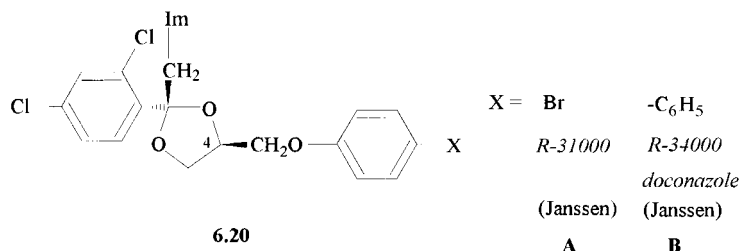


Thus, title 1,3-dioxolanes, for example **6.19**, have been claimed as antimycotics and fungicides (see also section 6.1.4.1).[6.118, 6.119, 6.120, 6.121, 6.122, 6.123, 6.124, 6.125, 6.126, 6.127]



They are effective bactericides and antimycotics, tested against vaginal candidiasis in rats, against *Trichophyton mentagrophytes* and *Aspergillus niger*. As fungicides they inhibit *Erysiphe cichoracearum* on cucumbers, *Botrytis cinerea* on beans and *Puccinia recondita*.

The *cis* form of a compound with biphenyl for R_s and $\text{C}_6\text{H}_4\text{COOCH}_2$ - as 4-substituent shows superior *in vitro* inhibition of *Candida albicans* compared with bifonazole and ketoconazole.[6.128] Isomeric structures with biphenyl = R' provided development candidates **6.20A**, R-31000 [59364-79-3] and doconazole.[6.080]

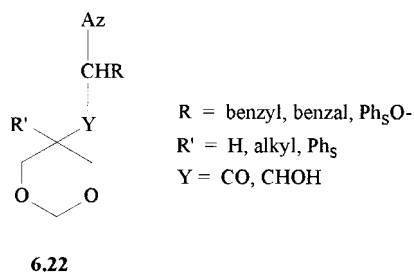
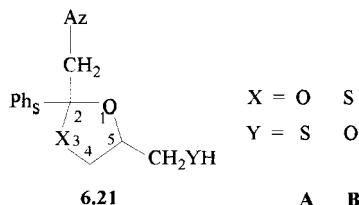


Doconazole, **6.20B** [59831-63-9] represents a systemic antifungal with oral activity against *Coccidioides immitis*.[6.129] Both of these potential antimycotics have apparently been superior to miconazole on oral dosing.

Finally, further substitution of X in **6.20** with basic groups brought the breakthrough with highly active piperazine derivatives resulting in ketoconazole and other mainly oral antimycotics (see section 6.2.2).

Corresponding 1,3-dioxolane-4-methanethiols **6.21A** and 1,3-oxathiolane-5-methanols **6.21B** have been described in a paper.[6.067]

Title 1,3-dioxanes like **6.22** have been claimed as fungicides.[6.130, 6.131, 6.132]

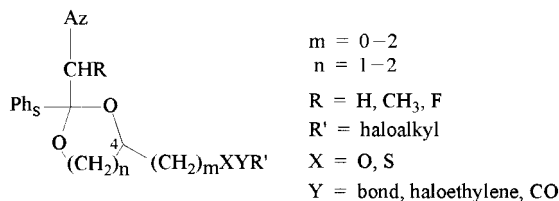


6.1.7.2 4-[2-(1*H*-Azol-1-yl)-1(hydroxy- or keto)alkyl]-1,3-dioxolanes

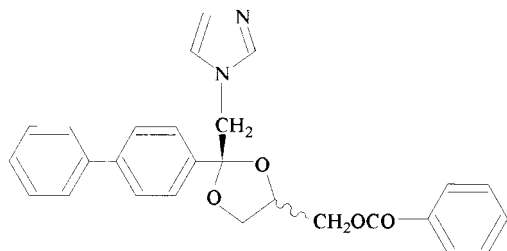
4-[2-(1*H*-Azol-1-yl)-1-hydroxyalkyl-1,3-dioxolanes have been claimed as antimycotics.[6.133, 6.134, 6.135]

6.1.8 2-(1*H*-Azol-1-yl)methyl-4-hydroxymethyl 1,3-dioxolanes and -dioxanes and their derivatives

Since phenylalkyl at C4 has been found interesting to maintain antifungal activity in the series of section 6.1.7.1, this substituent was further modified to Ph₅OCH₂- as shown in the general structure **6.23** as disclosed in patents,[6.136, 6.137, 6.138], and described in papers.[6.139, 6.140, 6.141, 6.142, 6.143, 6.144]



These antimycotics with activity against *Penicillium chrysogenum* and *Trichophyton rubrum* also control *Puccinia graminis* on wheat. Both *cis*- and *trans* biphenyl analogs and ester derivatives **6.24** show particular activity against *Candida albicans*. [6.144]

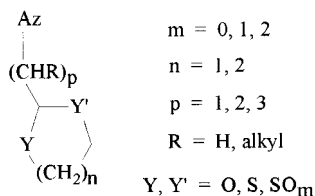
**6.24**

The *cis* isomer demonstrates optimal antifungal activity at pH 5.8, the *trans* form at pH 7.2.

Another ester derivative of the 4-hydroxymethyl group incorporates a partial structure of norfloxazine.[6.145]

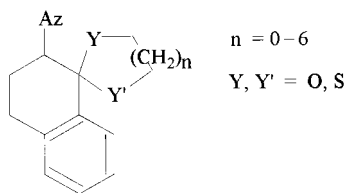
6.1.9 Thioanalogs of *x*-(1*H*-azol-1-yl)alkyl dioxacycloalkanes and their derivatives

Title compounds **6.25** have been claimed as fungicides.[6.146, 6.147, 6.148, 6.149, 6.150]

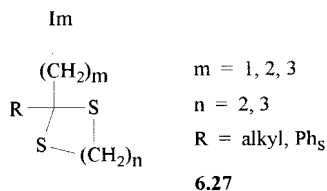
**6.25**

They control *Botrytis cinerea* on beans, *Erysiphe graminis* on barley and *E. cichoracearum* on cucumber.

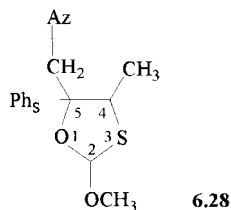
A cyclic example **6.26** is covered by one disclosure.[6.151]

**6.26**

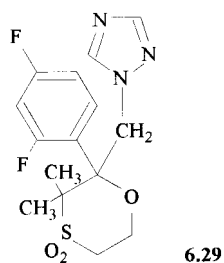
Dithiocycloalkanes **6.27** have been claimed as spermicides.[6.152]



4-(1*H*-Azol-1-yl)methyl-1,3-oxathianes like **6.28** or -oxathiolanes show superior efficacy in the *Candida albicans*-infected mouse model.[6.153]

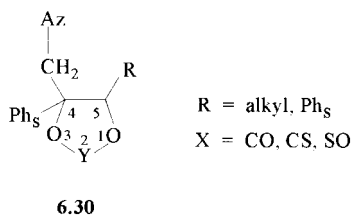


2-(1*H*-Triazol-1-yl)methyl-1,4-oxathiane **6.29** displays better efficacy against systemic candidiasis in mice than fluconazole.[6.103, 6.154]



6.1.10 4-(1*H*-Azol-1-yl)methyl-1,3-dioxolan-2-ones, 2-thiones and related compounds

Title compounds **6.30** have been claimed as fungicides.[6.104, 6.155]

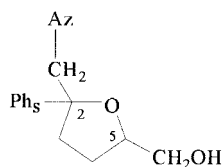


They display excellent *in vitro* activity against pseudomycelium formation of *Candida albicans*, against *Trichophyton asteroides*, and *in vivo* against systemic

murine candidiasis. However, little inhibition of *Aspergillus fumigatus* has been seen.[6.066]

6.1.11 *x*-(1*H*-Azol-1-yl) and *x*-(1*H*-azol-1-yl)methyl tetrahydrofurans and derivatives

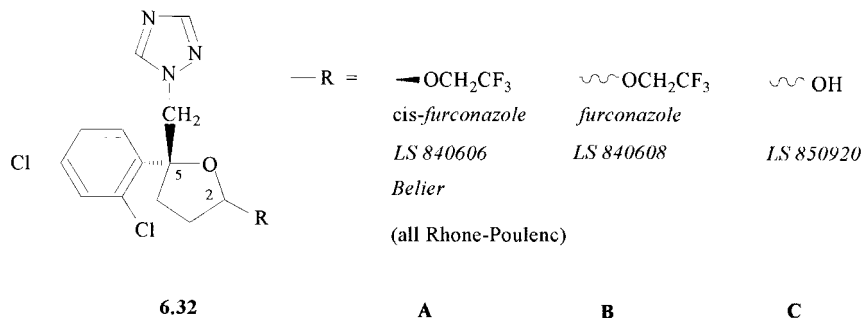
Title compounds include 2-(1-Azol-1-yl)methyl-tetrahydrofurans,[6.156] 2-(1*H*-azol-1-yl)methyl-5-hydroxy- or 5-hydroxymethyl-tetrahydrofurans like **6.31**,[6.157, 6.158, 6.159, 6.160, 6.161, 6.162], 3-(1*H*-azol-1-yl)methyl-3-hydroxy-tetrahydrofurans,[6.163] and 4-(1*H*-azol-1-yl)-2-hydroxy-tetrahydrofurans.[6.164]



6.31

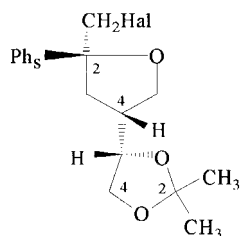
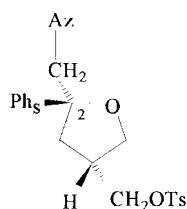
These compounds have been claimed as antimycotics and fungicides. They show excellent control of *Erysiphe Graminis* on barley without retarding the growth of the crop.

From these series furconazole **6.32**,[112839-33-5] in *cis*-form **6.32A**,[12839-32-4] has emerged as a fungicide for the control of ascomycetes, basidiomycetes and fungi imperfecti on cereals, vines, fruit trees and tropical crops.[6.165, 6.166, 6.167]

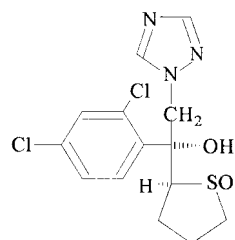


Labeled furconazole has been prepared from [U-¹⁴C]-aniline.[6.168] The active component has 2*RS*-5*RS*-conformation. Synthesis of radioactive furconazole through intermediates **6.32C**, LS 850920 and **6.32B**, LS 840608, uptake by wheat seedlings and its movement in soil have been studied,[6.168, 6.169, 6.170] but the product has been deleted from further development.[6.166]

Chiral intermediates **6.33** and **6.34** have been disclosed for the synthesis of antifungal agents such as Sch 51048 and Sch 56592 (see section 6.2.5). [6.171, 6.172, 6.173]

**6.33****6.34**

Tetrahydrothiolane derivatives **6.35** have been discovered which display, in spite of disappointing *in vitro* activity, equal efficacy against systemic *Candida albicans* infection of mice than ketoconazole. [6.174]

**6.35**

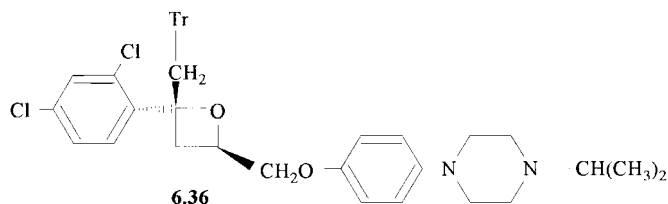
6.1.12 x-(1H-Azol-1-ylmethyl)tetrahydropyrans

Title compounds have been claimed as antibacterials, antifungals and antiprotozoals. [6.175, 6.176]

6.2 *x*-(1*H*-Azol-1-yl)alkyl-*y*-(hydroxy/ or aminoalkyl)-oxetanes, -1,3-dioxolanes, and -tetrahydrofuranes and their derivatives, with a further basic substituent

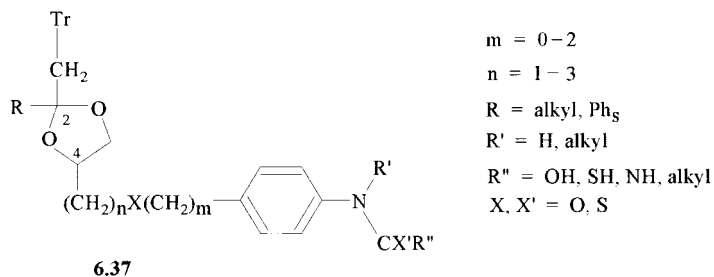
6.2.1 2-(1*H*-Azol-1-yl)methyl-2-phenyl-4-(4-[4-alkylpiperazin-1-yl]-pheno xymethyl)-oxetane

Title compound **6.36** inhibit *in vitro* *C. parapsilosis* and *C. albicans*. [6.177]



6.2.2 2-(1*H*-Azol-1-yl)methyl-4-(hydroxyalkyl)-1,3-dioxolanes, their thio analogs, derivatives and isomers, with a further basic substituent, excluding piperazine

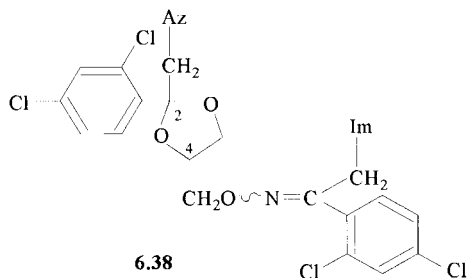
Title compounds **6.37** incorporate a second basic nitrogen group, or its derivative, exclusive of piperazine. [6.178].



They have been reported in disclosures as antibacterials, antimycotics and fungicides. [6.178, 6.179, 6.180, 6.181, 6.182, 6.183, 6.184, 6.185, 6.186]

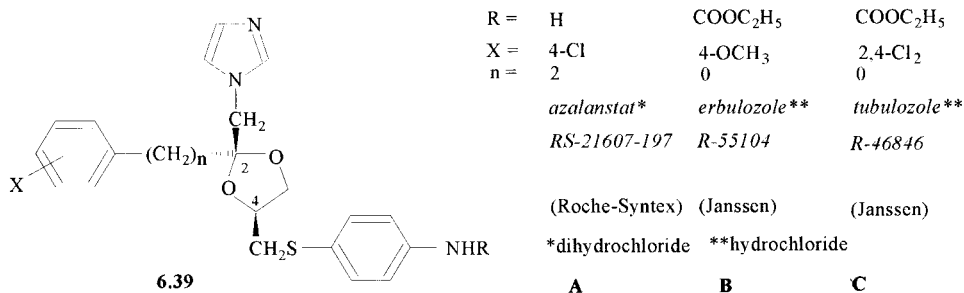
In a recent paper, larger than usual partial structures of itraconazole and oxiconazole have been combined to **6.38** which shows good *in vitro* activity against *C. albicans*, *A. flavus* and *F. solani*. [6.187]

Title substances **6.37** inhibit *Microsporium canis*, *Candida albicans* infection in mice, *M. gypseum*, *Saccharomyces pastorianus* and have also antitumor activity.



From the title series, azalanstat, erbulozole and tubulozole have been developed.

Azalanstat **6.39A** [143484-82-6; base 143393-27-5] proved to be a much more potent, selective inhibitor of lanosterol-14 α -demethylase than ketoconazole, but it has been developed as the first non-steroidal hypolipidemic with this route of action.[6.188]

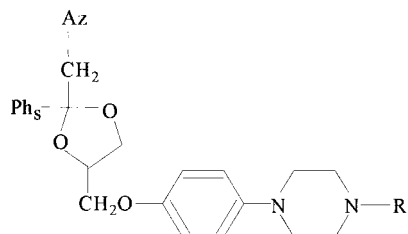


Erbulozole **6.39B**, [124784-31-4] prevents malignant invasion *in vitro* and exerts an antitumoral effect, such as against murine fibrosarcomas.[6.189] Erbulozole is more water-soluble than tubulozole, and it allows a clinically useful formulation as complex with cyclodextrines. It has also radioprotective activity.

The microtubule inhibitor **6.39C**, tubulozole [free base, 84697-22-3] acts against a wide range of transplantable neoplasms in experimental animals.[6.190] This activity is confined to the *cis* stereomer. The *trans*-stereomer may be useful for the treatment of cutaneous leishmaniasis.[6.190]

6.2.3 2-(1H-Azol-1-yl)methyl-4-(subst. phenoxyalkyl)-1,3-dioxolanes with piperazine as the basic substituent

Title compounds **6.40** have been claimed as bactericides, fungicides and protozoacides.[6.191, 6.192, 6.193, 6.194, 6.195, 6.196, 6.197, 6.198, 6.199, 6.200, 6.201, 6.202, 6.203, 6.204, 6.205, 6.206, 6.207, 6.208, 6.209, 6.210, 6.211, 6.212, 6.213, 6.214, 6.215]



R = acyl, Ph₈, Ph₈alkyl,
pyrimidyl, alkoxyimidecarbonyl,
triazolonyl, ethoxycarbonyl

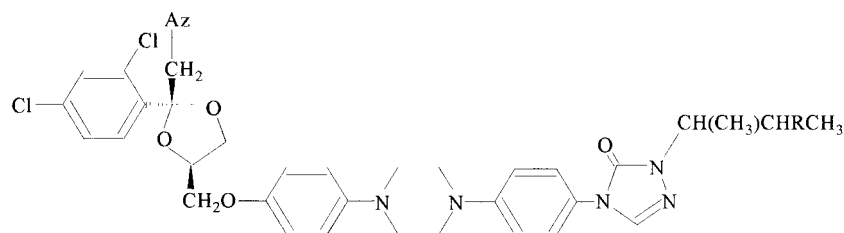
6.40

Some papers also describe the synthesis of derivatives with Ar = biphenyl-4-, [6.216] with R² = benzoxazolone-5-yl, [6.217] and with 4-(N-cycloalkylcarbamoyl), [6.218]

From these series itraconazole, ketoconazole, saperconazole and terconazole have been developed.

6.2.3.1 Itraconazole: Reviews, chemical, analytical and pharmaceutical aspects

Itraconazole **6.41A**, [84625-61-6] an orally administered antifungal agent, has been developed as a successor of ketoconazole, a need soon felt after the latter was marketed. [6.219, 6.220, 6.221, 6.222, 6.223, 6.224, 6.225, 6.226, 6.227, 6.228, 6.229, 6.230, 6.231, 6.232]



6.41

Az =			Tr
R =	H	H	OH
	<i>R</i> -51211	<i>R</i> -49960	<i>R</i> -63372
	<i>Itraconazole</i>		<i>hydroxy-</i>
	<i>Oriconazole</i>		<i>itraconazole</i>
	<i>Sporanox</i>		
	(Janssen)	(Janssen)	(Janssen)
	A	B	C

The agent has been reappraised for the therapy of superficial fungal infections. [6.232]

Branching of the N²-alkyl of the 3*H*-1,2,4-triazol-3-one gave the final, dramatic increase in two models of animal mycosis. An imidazole analog **6.41B**, R 49960 of itraconazole, as well as the triazole analog **6.42D**, R 42164 of ketoconazole, proved to be impressively inferior. [6.222]

A number of congeners of itraconazole have been studied.[6.228]

Pure stereoisomers of itraconazole have been claimed to be more water-soluble than the diastereomeric mixture.[6.233]

Chromatographic and microbial methods have been used for the determination of itraconazole and its metabolite hydroxyitraconazole R 63372.[6.234, 6.235, 6.236, 6.237, 6.238, 6.239, 6.240, 6.241, 6.242, 6.243, 6.244, 6.245]

The solubility of itraconazole is rather low in water and in organic solvents, except in DMF, THF and DMSO.[6.226]

Hydroxypropyl- β -cyclodextrin greatly enhances peak concentration and area under concentration—time curve as determined by bioassay.[6.246] Incorporation of the drug in dipalmitoyl phosphatidylcholine liposomes improves drug levels in lung, brain and liver even more and may be helpful in the treatment of systemic mycoses such as cryptococcosis and pulmonary aspergillosis.[6.247, 6.248] Variable bioavailability in the immunocompromised state presents a certain disadvantage,[6.249, 6.250] which should be overcome by the intravenous formulation with hydroxy- β -cyclodextrin, now in development specifically for hematology and intensive care patients.[6.251]

6.2.3.2 Itraconazole: Preclinical and clinical results

In vitro and *in vivo* antifungal activities of itraconazole are poorly correlated. In a series of 36 related compounds, *in vivo* tests with ketoconazole as standard show six substances clearly superior against vaginal candidiasis in rats, and eight substances clearly superior against microsporosis in guinea pigs.[6.220] Itraconazole has been compared systematically with ketoconazole.[6.252]

For *in vitro* and *in vivo* activities and clinical experience, see symposia reports and reviews.[6.219, 6.220, 6.221, 6.222, 6.223, 6.224, 6.225, 6.226, 6.227, 6.228, 6.229, 6.230, 6.231, 6.232, 6.253, 6.254]

In vitro superiority of itraconazole against fluconazole-resistant isolates of *Candida* spp. and clinical isolates from patients with pulmonary aspergillosis have been demonstrated recently,[6.255, 6.256] as well as against many experimental mycoses.[6.257, 6.258] Itraconazole is 100-fold more active against *Aspergillus* strains,[6.259, 6.260] and 10-fold more active against *Pityrosporum ovale* than ketoconazole.[6.261]

Both itraconazole and ketoconazole inhibit *in vitro* *Leishmania mexicana mexicana*. [6.262] Pharmacokinetics has been studied extensively and compared with that of fluconazole and ketoconazole. [6.263, 6.264, 6.265, 6.266, 6.267, 6.268, 6.269, 6.270] The antifungal activity of the metabolite hydroxyitraconazole **6.41C**, comes close to that of itraconazole.[6.243, 6.271]

First clinical experience has demonstrated the potential of itraconazole.[6.221, 6.223, 6.272] This drug represents a major step forward in the treatment of aspergillosis.[6.273] Acute, disseminated and semi-invasive pulmonary forms respond

extremely well.[6.274, 6.275, 6.276, 6.277, 6.278, 6.314] For the invasive form, itraconazole is a useful alternative for amphotericin B.[6.279, 6.280] Chronic, endocardial and cerebral forms respond to high doses. [6.280, 6.281, 6.282, 6.283, 6.284, 6.285] The drug also promises to be useful in the prophylaxis of vaginal, systemic and disseminated *Candida* infections and systemic, invasive aspergillosis. [6.286, 6.287]

Against moderate blastomycosis and histoplasmosis without CNS involvement, itraconazole is the drug of choice. It has largely replaced amphotericin B for maintenance therapy.[6.273, 6.274, 6.276, 6.277, 6.288, 6.289, 6.290, 6.291]

Vaginal and systemic candidiasis is cured with itraconazole. [6.273, 6.274, 6.276, 6.290] This drug is also recommended for the treatment of chronic and esophageal candidiasis with serious underlying conditions,[6.292] and appears useful for prophylaxis in high-risk immunocompromised patients.[6.274]

Chromomycosis (Chromoblastomycosis) caused by *Cladosporium carionii* responds very well; against *Fonsecaea pedrosoi* as the causative agent, long-term therapy is indicated.[6.274, 6.293]

Cutaneous cryptococcosis responds well to itraconazole.[6.294, 6.295, 6.314] Extrameningeal, pulmonary and generalized cryptococcosis show a 100% complete response.[6.273, 6.277] In cryptococcal meningitis, about two-thirds of patients enjoy a complete response.[6.273, 6.276, 6.284]

About two-thirds of patients suffering from leishmaniasis, caused by *L. brasiliensis* respond to itraconazole after 1–2 months of treatment.[6.274]

In paracoccidiomycosis, 96% of the patients enjoyed cure or marked improvement after 3–6 months of treatment with itraconazole. The drug can be given in much lower doses, and shows a faster onset of action than ketoconazole.[6.274] In the treatment of *Coccidioides immitis* infection, life-long treatment with itraconazole (or another oral azole antimycotic) is indicated to avoid fatal relapse, even after apparent cure.[6.296]

Against *Pityriasis versicolor*, a total doses of 1 g itraconazole cured 77–84% of the patients after 3–4 weeks.[6.274, 6.219, 6.297]

Itraconazole promises to be a major therapeutic tool in the treatment of systemic sporotrichosis. [6.273, 6.274, 6.276, 6.293, 6.314]

Chronic skin dermatoses caused by *Trichophyton rubrum* give a very good response to itraconazole which allows shorter treatment than ketoconazole. [6.221, 6.274, 6.276, 6.298] Guinea pigs infected by *Trichophyton mentagrophytes* or *Microsporum canis*, on oral treatment with itraconazole, were cleared of the fungus not only located in the stratum corneum but also in hair sheets; the latter site is hardly accessible through topical treatment.[6.299] Onychomycosis responds very well to itraconazole,[6.300] with monthly cycles of 1-week pulse therapy as a possible regimen.[6.301] Successful treatment of tinea pedis and tinea manuum has been demonstrated.[6.302]

6.2.3.3 Itraconazole: Resistance, safety and side effects

Resistance against fluconazole, as encountered in AIDS patients, may possibly be overcome by treatment with itraconazole,[6.303] but resistance against itraconazole

may develop thereafter. This has given rise to a pessimistic view on long-term azole therapy of mucosal candidiasis for these patients.[6.304] Immunocompromized cancer and transplantation patients can be protected from fungal infection by itraconazole.[6.305, 6.306]

Safety aspects and adverse patient reactions of the drug have been reviewed.[6.227, 6.307, 6.308, 6.309] It is important to note that ketoconazole inhibits testosterone formation in rat testes subcellular fractions, while itraconazole does not.[6.310, 6.311] Itraconazole decreases humoral and cell-mediated immune responses in mice.[6.312]

In the clinical trials discussed above, 2–3.5% of the patients report minor side effects such as nausea, pyrosis, mild gastrointestinal intolerance and headache in the treatment of skin dermatoses, pityriasis versicolor and vaginal candidiasis. Their incidence increases to about 8% in the treatment of systemic mycoses, caused by longer treatment, by the character of the disease, and by elevated liver enzymes.[6.274, 6.313]

Since itraconazole is potentially teratogenic in rats, proper precautions have to be taken in the treatment in women of child-bearing age.[6.227, 6.274]

Itraconazole displays lipophilic character, which is partly responsible for the easy penetration of biological membranes and the inhibition of membrane-bound enzymes. Tissue concentration is much higher than in plasma, the half-life of about one day is relatively long, and biotransformation in the liver results in a large number of inactive metabolites. High levels in the skin and mucous membranes result in a depot effect of these tissues, from which the drug does not leak back into plasma. Itraconazole does not affect hepatic P-450-dependent drug metabolism in the rat, in contrast to ketoconazole and miconazole. It does not cause hepatitis.[6.272, 6.274, 6.294, 6.303, 6.306]

6.2.3.4 Ketoconazole: Reviews, chemical, analytical and pharmaceutical aspects

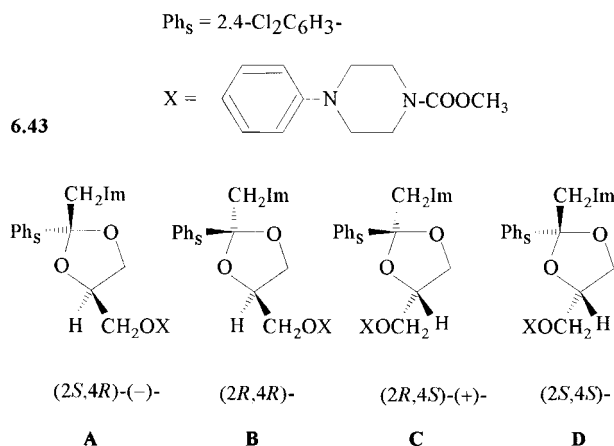
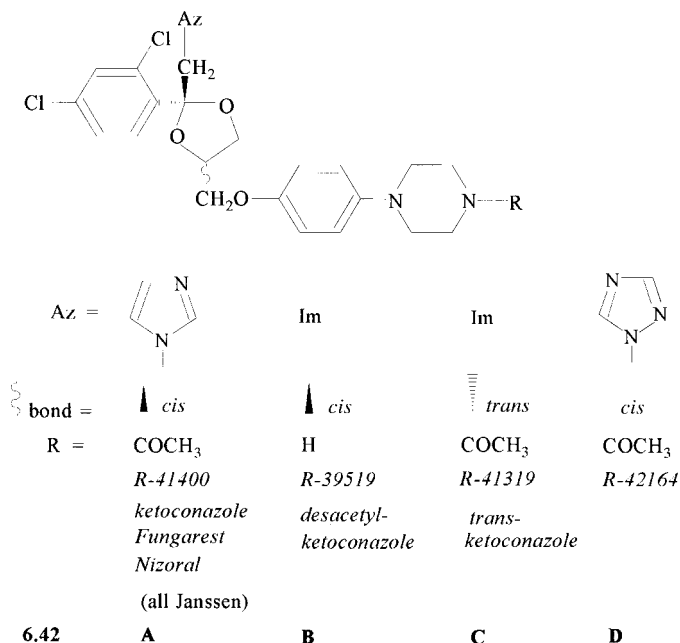
Ketoconazole **6.42A**, [65277-42-1] represents the first successful oral antimycotic and is outstanding as the most thoroughly investigated agent among antifungal azoles.[6.315, 6.316].

Its synthesis has been reinvestigated.[6.317, 6.318]

The desacetyl derivative **6.42B** and the *trans* isomer **6.42C** are less antifungal than ketoconazole itself.[6.319] Partial structures of the four stereoisomers are **6.43A** to **6.43D**; the prescribed drug is a racemic mixture of *cis*-isomers **6.43A** and **6.43C**.[6.320]

Synthesis of the diastereoisomeric ketoconazoles can be achieved from diastereomerically pure 4-tosyloxymethyl- or 4-mesyloxymethyl-dioxolanes, [6.320, 6.321, 6.322] or from (*R*)- and (*S*)-epichlorhydrin.[6.323]

Analytical determination methods for ketoconazole have been described using HPLC,[6.324, 6.325, 6.326, 6.327, 6.328, 6.329, 6.330, 6.331, 6.332, 6.333] spectrofluorometry,[6.333, 6.334, 6.335, 6.336, 6.337, 6.338, 6.339] NMR,[6.339, 6.340] or electrochemistry.[6.332, 6.333, 6.339]



Good absorption of an oral dose of ketoconazole requires sufficiently low gastric pH to dissolve in the gastric juice,[6.341] though *in vitro* the disintegration time of ketoconazole tablets does not change between pH 2 and pH 6.[6.342] An acidic beverage, like Coca-Cola, significantly increases the absorption of the drug.[6.343] Surprisingly, optimal cellular uptake of ketoconazole by *Candida albicans* occurs

between pH 6.5 and 7.0 when both the imidazole and the piperazine moieties are not protonated.[6.344] The molecular basis for the pH-dependent activity of ketoconazole against *C. albicans* cannot be attributed to altered drug transport.[6.345] Combining ketoconazole with glutamic acid hydrochloride prevents a decrease of the absorption of an oral dose after food intake.[6.346] There seems to be no systemic absorption from a single vaginal dose of ketoconazole.[6.347]

With an oral dose, ketoconazole is dispatched to the stratum corneum.[6.348] The stability of oily eye drops of ketoconazole on heat sterilization and of ethanolic solutions have been demonstrated.[6.349, 6.350] Dimethylsulfoxide enhances the penetration of the drug across the blood—brain barrier in mice.[6.351]

Ketoconazole oleate incorporated in low density lipoproteins improves the control of leishmaniasis.[6.352] Compositions for topical treatment with ketoconazole of acne vulgaris and of alopecia have been proposed.[6.353, 6.354]

Bioavailability of rectal ketoconazole suppositories has been compared with that of oral medication.[6.354]

6.2.3.5 Ketoconazole: Preclinical and clinical aspects

Many symposia and reviews report on *in vitro*, *in vivo* and clinical results with ketoconazole.[6.316, 6.356, 6.357, 6.358, 6.359, 6.360, 6.361, 6.362, 6.363, 6.364, 6.365, 6.366, 6.369, 6.368] Here, we rather discuss below the unexpected activities and side effects since this still interesting molecule must also be considered as a lead structure to drug classes with other than antifungal activities.

The *cis* racemic mixture of **6.43A** and **6.43C** has been found to be a more potent inhibitor of mammalian lanosterol 14-demethylase than the *trans* isomers **6.43B** and **6.43D**. Stereomer **A** is three times more active than its antipode **C**. In the inhibition of progesterone 17,20-lyase, this factor may reach 40. Significant selectivity against 11 other cytochrome P-450 enzymes has been demonstrated.

For the treatment of hormone-dependent prostate cancer, there seems to be no advantage in using enantiomerically pure *cis* compound.[6.320]

Ketoconazole proved fungicidal against zoophilic fungal pathogens such as *Trichophyton verrucosum*, *Pityrosporon canis*, *Cryptococcus neoformans* and *Torulopsis famata*.[6.369]

Ketoconazole is by far the most active agent against *Malassezia furfur* *in vitro* and *in vivo*, when compared with five other standard antimycotics.[6.370]

Ketoconazole inhibits *in vitro* the growth of *Leishmania mexicana mexicana* promastigotes, and *L. major*.[6.371, 6.372] It effectively controls *L. m. amazonensis* infections of mice,[6.373, 6.374] and *L. donovani* infections in the hamster.[6.375] Amino acid derivatives (such as phenyl alanyl) of ketoconazole and oleyl ketoconazole are particularly active. [6.374]

Trichinella spiralis infection of mice is controlled by ketoconazole.[6.376]

The efficacy of ketoconazole against *Trypanosoma cruzi*, the causative agent of Chagas disease, has been studied thoroughly.[6.377, 6.378, 6.379, 6.380, 6.380a] A summary of earlier work on the antiprotozoal activity of ketoconazole, including reduction of liver necroses caused by *Entamoeba histolytica*, has appeared.[6.378]

6.2.3.6 Ketoconazole: Safety and side reactions

Safety aspects of ketoconazole have been reviewed.[6.381] Hepatotoxicity emerged as one of the main factors why a replacement for ketoconazole had to be sought. The drug shows a relatively high teratogenic potential.[6.382]

Gynecomastia detected as a side effect of ketoconazole treatment led to a thorough investigation of its interference with sterol metabolism; as a consequence, treatment of human breast cancer,[6.383, 6.384] human pancreatic carcinoma,[6.384] human colonic adenocarcinoma, [6.384, 6.385] and leukemia has been attempted.[6.384, 6.386] Beneficial effects of ketoconazole on melanoma tumor,[6.387] rat pituitary cells,[6.388] and on the metastasis of pancreatic adenocarcinoma have been seen.[6.389] In particular, treatment of human prostate cancer,[6.320, 6.383, 6.384, 6.390, 6.391, 6.392] seems hopeful, though the drug has not been generally accepted as a remedy for hormone-related cancers.[6.392] The potential activity against the latter is connected with a transient decrease of plasma testosterone and 4-androstenedione levels during treatment, and an increase in plasma 17-hydroxyprogesterone after a high-doses regime of ketoconazole.

Nonetheless, studies on the influence of ketoconazole on the biochemistry of human steroids continue.[6.393, 6.394, 6.395, 6.396, 6.397, 6.398, 6.399, 6.400, 6.401, 6.402, 6.403, 6.404, 6.405, 6.406, 6.407, 6.408, 6.409, 6.410]

Ketoconazole exerts antithyroid activity,[6.411] reduces elevated cortisol levels,[6.412] and suppresses adrenal and gonadal androgen biosynthesis.[6.413]

Ketoconazole has spermicidal activity, but appears too toxic for use as a contraceptive in men.[6.414, 6.415, 6.416, 6.417]

Ketoconazole interferes with cholesterol synthesis and metabolism,[6.418, 6.419, 6.420, 6.421, 6.422, 6.423, 6.424] which seems to be the cause of liver damage after prolonged use of the drug,[6.424, 6.425, 6.426, 6.427, 6.428, 6.429, 6.430] as well as its own impaired metabolism and of the metabolism of other drugs.[6.428, 6.431, 6.432]

Ketoconazole exerts a beneficial effect on Cushing's disease due to suppression of adrenal cortisone. [6.433] Ketoconazole and some compounds with closely related structures are effective in the treatment of diabetes mellitus type II.[6.434]

Ketoconazole impairs the metabolism, and thus increases the toxicity of the immunosuppressant cyclosporin which may need to be co-administered.[6.431, 6.435, 6.436, 6.437, 6.438, 6.439, 6.440] In fact, the cyclosporin dose can be reduced by two-thirds during ketoconazole treatment of transplantation patients.[6.441]

General and clinical pharmacokinetics of ketoconazole have been reviewed and compared with that of fluconazole and itraconazole.[6.270]

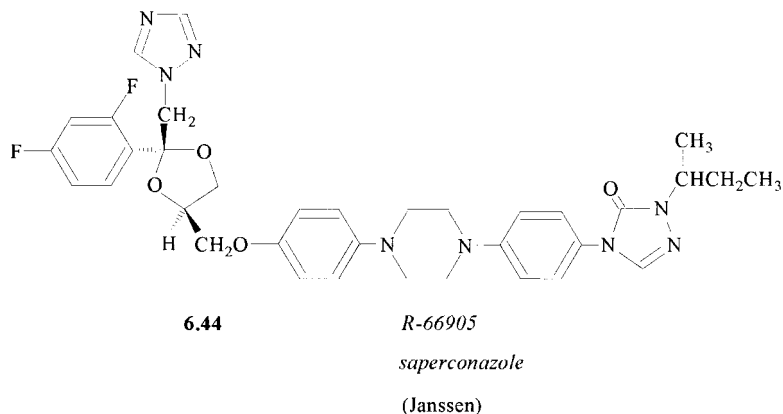
N-Deacetylated ketoconazole **6.42B** has been isolated as a metabolite from mouse or rat liver.[6.442, 6.443, 6.444] Ketoconazole-induced phospholipidosis in the mouse is associated more with **6.42B** than with the parent drug.[6.445] This

metabolite is 15-to 50-fold more active against *Plasmodium falciparum* than the parent drug.[6.446]

Details of the 1,2,4-triazol-analog R 42164 of ketoconazole, compound **6.42D**, [6.222] have been reported.

6.2.3.7 Saperconazole and terconazole

Saperconazole **6.44**, [110588-57-3] was developed as a successor for ketoconazole.[6.447]



In vitro activity against 234 species of fungi with a total of 2775 strains demonstrated >95% inhibition in the range of 0.1 to 1.0 µg/mL with most species, except *Fusarium* and *Zygomycetes*. [6.448, 6.449]

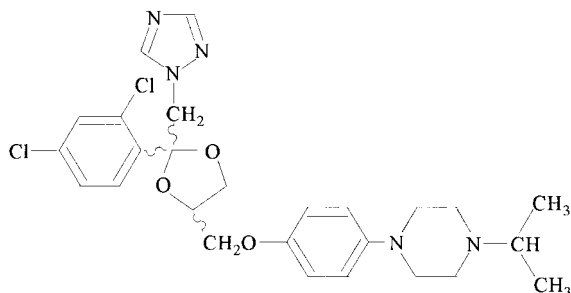
In vivo, the drug is highly effective in the treatment of microsporosis, trichophytosis, skin dermatoses, vaginal candidiasis, pityrosporiasis, keratomycosis (caused by *C. albicans*, *F. moniliforme*, *A. flavus*), sporotrichosis, systemic candidiasis, meningocerebral and generalized cryptococcosis, and aspergillosis. Infections by *Fusarium*, *Zygomycetes* (*Mycor*, *Rhizopus*, *Syncephalastrum*), *Actinomycetes* as well as from bacteria however cannot be influenced with concentrations <10 µg/mL. [6.450]

Solubility of saperconazole in water, ethanol and 0.1M HCl is relatively low; in polyethylene glycol 400 it amounts to 0.6 g/100 ml solution and in DMSO to 4.1 g/100 ml. [6.447] After solubilization with hydroxypropyl-β-cyclodextrin, an oral dose of saperconazole markedly improves serum concentration. [6.246]

Saperconazole is not affected by immunodepressing agents. It is very effective in vaginal and systemic candidiasis in immunocompromised animals, and in topical treatment of guinea pigs infected by *Trychophyton mentagrophytes*. [6.314] Thus, saperconazole appeared, with its superiority over fluconazole, to be a new addition to the small armory of agents against *Aspergillus* and *sporotrichosis* infections.

Saperconazole is however inferior to ketoconazole as an inhibitor of *Torulopsis glabrata*. [6.448] After ovarian tumors were induced in rats given a 10-fold therapeutic dose, further development has been suspended. [6.451]

Terconazole **6.45**, [67915-31-5] has been developed as a topical antimycotic. [6.452]

**6.45**

R-42470
(±)
terconazole
triaconazole
Fungistat
(Janssen, Cilag)

Stereoselective syntheses of (+)-(2*R*,4*S*)- and (–)-(2*S*,4*R*)-terconazole have been described. [6.453] Hydrolysis cleaves the cyclic ketal to produce 1-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-ethanone which shows antibacterial and antimycotic activity. [6.454]

At 100 µg/mL, (±)-terconazole also represents a bacteriostatic agent, with activity against *Salmonella pullorum* and *Streptococcus pyogenes*. It has therapeutic potential in experimental candidiasis in rats, experimental trichophytosis and microsporosis in guinea pigs. On oral dosage, however, terconazole is less active than ketoconazole. [6.455]

The planning and execution of this first attempt to improve ketoconazole teaches us much about contemporary antimycotic medicinal chemistry, and outlines standards which must now be met by any such drug development program. Guidance has come from the following basic observations and assumptions. [6.455, 6.456]

1. The inhibitory effect of azole compounds on fungal cytochrome P-450 (named after its absorption maximum at 450 nm) can be improved by replacement of 1,2,4-triazole for imidazole. Thus, the affinity of the triazoles N-4 for the heme iron of P-450 is enlarged compared with that of the imidazoles N-3. This increases metabolic stability against oxidation and prolongs the intracellular availability of the agent.
2. First-generation azole antimycotics such as clotrimazole can accelerate their own metabolism by inducing liver enzymes, thus reducing the therapeutic effect during systemic therapy. In addition, P-450 isoenzymes play a role in the metabolic breakdown of xenobiotics in the skin and in vaginal tissue, which may in consequence lead to higher side effects. Therefore, improved selectivity of any new antifungal

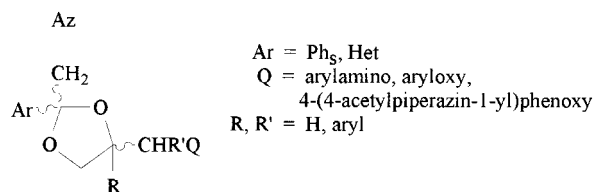
agent would mean first of all, improved selectivity for the *fungal* cytochrome P-450, and thus improve the safety of the proposed drug.

3. The fungal membrane as the site of azole action should harbor the antifungal agent longer in order to extend temporally its action. This requires both lipophilic characteristics of the drug and a surface of similar dimensions to arrange in the bilayer of phospholipid molecules of the membrane. [6.456] Thus, in its inhibitory action of P-450, terconazole might mimic a phospholipid molecule.

However, despite these considerations, suspension of the clinical use of terconazole vaginal suppositories (160 mg) due to the high number of adverse side effects could not be prevented.[6.457]

6.2.4 4-(1*H*-Azol-1-yl)methyl-2-(subst. phenoxy-alkyl)-1,3-dioxolanes with piperazine as second basic substituent

Only one disclosure has been located for antifungal title compounds **6.46**. [6.458]

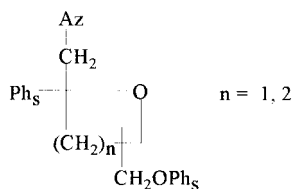


6.46

In this series, antiallergic and immunomodulating activities have also been seen, which suggest use for the treatment of hyperproliferative skin conditions.

6.2.5 2-(1*H*-Azol-1-yl)methyl-2-subst. phenyl-4-subst. piperazinephenoxy-methyl]-tetrahydrofurane derivatives

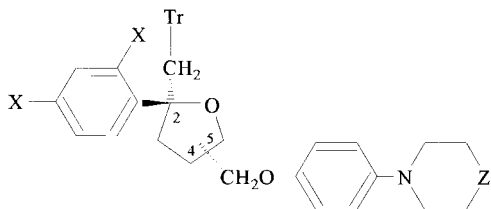
Title compounds of structure **6.47** have been claimed as fungicides.[6.459]



6.47

Their synthesis has been improved via Sharpless asymmetric dihydroxylation.[6.460]

From these, the five compounds **6.48A** to **6.48E**, which differ mainly by the Z-substituent, have been studied more closely.



furanyl-	4-	4-	4-	5-	5-
X =	2,4-F ₂	2,4-F ₂	2,4-F ₂	2,4-Cl ₂	2,4-Cl ₂
R =	N-CH(CH ₃) ₂	N-CH(CH ₃) ₂	N-CH(CH ₃) ₂	N-CH(CH ₃) ₂	SO ₂
	(-)	(+)	(±)	(±)	(±)
	Sch 45450	Sch 45449	Sch 42538	Sch 38918	Sch 42529
(all Schering-Plough)					

6.48 **A** **B** **C** **D** **E**

They include Sch 45450, **6.48A**; Sch 45449, **6.48B**; Sch 42538, **6.48C**; Sch 38918, **6.48D**; and the thiomorpholino analog Sch 42529, **6.48E** [6.460, 6.461, 6.462].

Agents **D** and **E** can be prepared starting with an aqueous Diels—Alder addition of halogenated 2-arylfurans to acetylenedicarboxylates.[6.462] Both are superior to ketoconazole *in vivo*.[6.462]

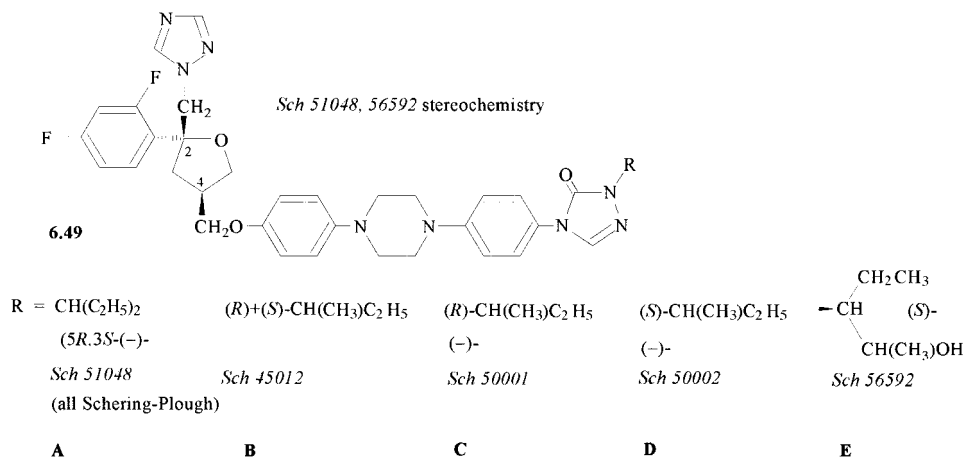
Optical resolution of agent **C** provided the more active eutomer **A** and the less active dystomer **B**.[6.461]

Further modifications **6.49C** of the title compounds carry a triazolone substituent at the end of the 4-phenylpiperazine side chain.[6.463] Again, five closely related substances **6.49A** to **6.49E** have been compared (see also section 6.1.11).[6.175, 6.465, 6.466]

Compound **6.49A**, Sch 51048 [161531-65-6] represents a broad-spectrum orally active antimycotic. A convenient synthesis starts from the *cis*-(-)-(2*R*)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-4-tosyloxymethyl-tetrahydrofuran.[6.173, 6.465, 6.466]

Sch 51048 is similar in activity to itraconazole and saperconazole, but superior to fluconazole in respect to fluconazole-resistant strains of *Candida krusei*, which causes hematogenous infection.[6.464, 6.465] This is outstanding for triazoles. *In vitro*, it is also superior to these three standards against *Blastomyces dermatitis*, and *in vivo*, after p.o. doses, against vaginal candidiasis.[6.464, 6.465]

In curative, p.o. treatment of pulmonary and systemic aspergillosis, the superiority of Sch 51048 over itraconazole, saperconazole and fluconazole has been considered most important.[6.467] Against murine blastomycosis, histoplasmosis and coccidioidomycosis, Sch 51048 is again superior to itraconazole or fluconazole.[6.465, 6.468]



However, Sch 51048 displays poor activity against *Candida glabrata*. [6.465]

Pharmacokinetic studies show interesting half-lives in mice, rats, dogs and monkeys. However, again, Sch 51048 had to be discontinued in favor of the more recent compound Sch 56592 (see below). [6.469]

Sch 50001, **6.49C** and its eutomer Sch 50002, **6.49D** represent the enantiomers of Sch 45012, **6.49B** and have been derived from the key (-)-2*R*-*cis*-tosylate intermediate **6.34**. [6.173, 6.461]

Sch 50002 has been demonstrated as the most active stereomer against *C. albicans* and *A. flavus* infection models. Terminal groups R were selected from alkyl, haloalkyl, aminoalkyl and CH₂COOH groups. Even with closely related R substituents like isopropyl (Sch 51047) or cyclopentyl (Sch 51767), a similar *in vivo* activity could not be realized. Sch 50002 closely approaches 51048 in the treatment of candidiasis in normal and immunocompromized mice. [6.461, 6.464]

Further modification of the terminal substituent of the lipophilic substituent at C-3 of the tetrahydrofuran has resulted, again from the same precursor **6.34**, in Sch 56592, **6.49E** [171228-49-2], selected as the successor of Sch 51048. [6.469, 6.470]

In vitro, the potential antimycotic Sch 56592 is superior to fluconazole, itraconazole and amphotericin B against pulmonary aspergillosis in mice. *In vivo*, superior efficacy has been demonstrated against infections of *Aspergillus fumigatus*, *A. flavus*, *Triptophyton mentagrophytes* and against vaginal candidiasis. Bioavailability has been demonstrated (in %) as 47 (mice), 49 (rat), 24 (dog), 22 (monkey). The maximum half-life has been determined as 22 hours in monkeys and 18 hours in dogs. This promising agent seems to carry hope as a cure for *Cryptococcus neoformans* infections. [6.470, 6.471]

7 1H-Azol-1-yl-boron, -silicon, -germanium, tin-, phosphorus-, oxygen and sulfur compounds

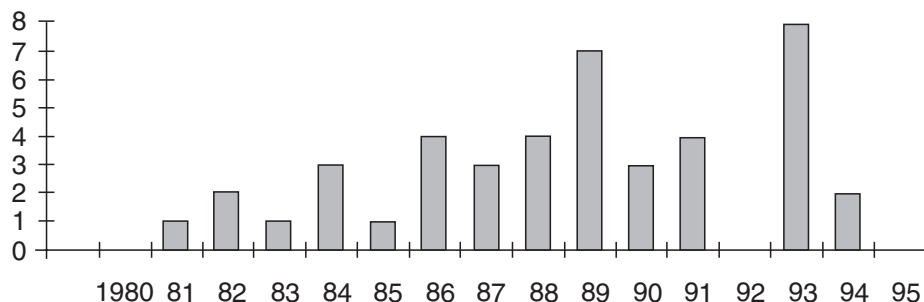
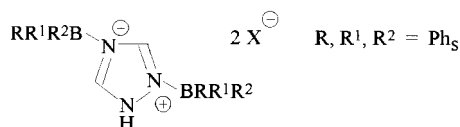


Fig. 7.1 Chronology of 43 patent applications of Chapter 7.

7.1 1H-Azol-1-yl boron compounds

Fungicidal diarylboron esters, thioesters,[7.001] and bis(triphenyl)boran-triazolium compounds **7.01** have been claimed which control *Erysiphe polygoni* on beans.[7.002]



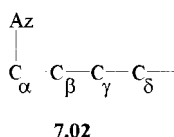
7.01

7.2 1H-Azol-1-yl organosilicon compounds and their hydroxy derivatives

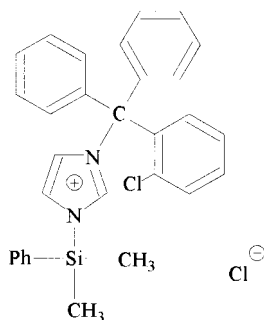
7.2.1 (1H-Azol-1-yl) organosilicon compounds without further functions

Sila substitution as a strategy for drug design has been reviewed.[7.003] A number of carbon/silicon pairs of drugs show that this exchange does not alter pharmacodynamics qualitatively, but may modify potency, selectivity, pharmacokinetics and toxicity. This principle has been applied to the synthesis of agrochemicals.[7.004]

Thus, in our title silylalkylazoles, silicon replaces one of the carbon atoms of the backbone alkyl group **7.02**.

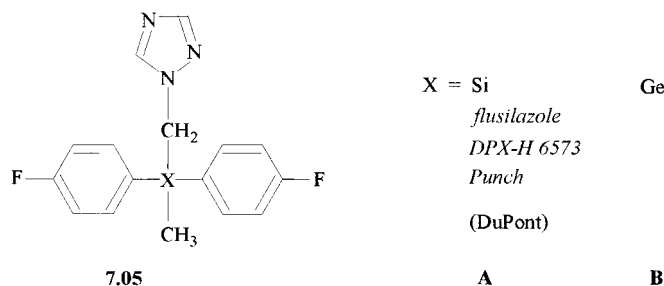
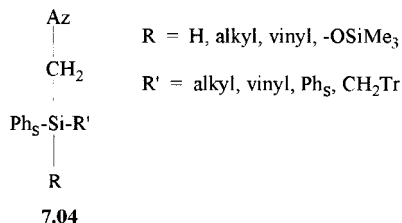


For example, α -silylalkyl-azoles have been claimed as antibiotics.[7.005] A quaternary silicon analog **7.03** of clotrimazole shows a broad antibacterial spectrum and antimycotic action combined with low skin irritation.[7.006]



β -Silylalkyl azoles such as **7.04** have been reported in several applications.[7.007, 7.008, 7.009, 7.010, 7.011, 7.012, 7.013, 7.014, 7.015, 7.016, 7.017] and have been discussed in a number of papers. [7.004, 7.018, 7.019, 7.020, 7.021, 7.022]

Unwanted 4-alkylated 4H-1,2,4-triazoles as by-products can be eliminated by heat treatment.[7.023] From these series, flusilazole **7.05A**, [85509-19-9] has evolved as broad-spectrum systemic, curative and preventive fungicide.[7.004, 7.024, 7.025]



Its development has been rationalized by a first screen (% preventive control at 100 ppm of cucumber powdery mildew, apple scab, peanut early leaf spot, and leaf rust) and by a second screen (ED₉₀ in g/ha against the same diseases).[7.004]

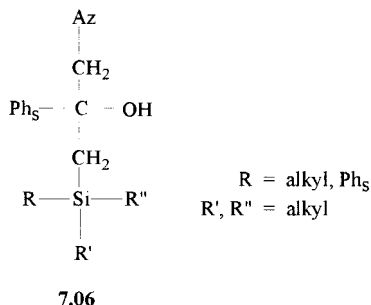
Aqueous solubility of flusilazole at 20°C amounts to 45 mg/L at pH 7.8 and 900 mg/L at pH 1.1. The agent is readily soluble in many organic solvents.[7.024, 7.025] A propylene solution has been proposed for decreased eye irritation.[7.026] The agent shows remarkable wash-off resistance.[7.027]

Flusilazole acts as potent inhibitor of the lanosterol 14α-demethylase enzyme of ergosterol and cholesterol biosynthesis.[7.028, 7.029] It is active against Ascomycetes, Basidiomycetes and Deuteromycetes. It controls certain species of *Cercospora beticola*, *Pseudocercospora herpotrichoides* and *Verticillium inaequalis* which are resistant to fluconazole.[7.030, 7.031, 7.032] Against *V. inaequalis*, flusilazole is over four times more active than myclobutanil.[7.033] In the control of foot rot, flusilazole outperforms prochloraz, and against fruit diseases it is superior to bitertanol. [7.004]

Flusilazole is not active against *Phycomycetes*, which do not have ergosterol in their cell membranes.[7.004]

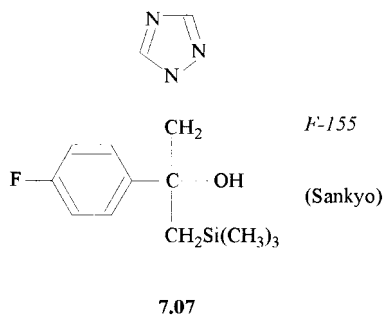
7.2.2 (1H-Azol-1-yl)-organosilicon compounds with a hydroxyl, silyloxy or cyano group

1-Azol-1-yl-x-hydroxy-y-silylalkyl compounds **7.06**, also called oxygenated silanes and their ethers have been claimed as antimycotics and fungicides,[7.023, 7.034, 7.035, 7.036, 7.037, 7.038] and reported in papers.[7.004, 7.039, 7.040]

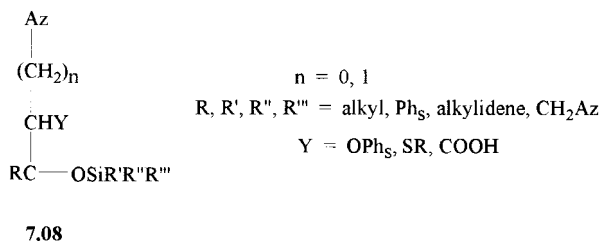


These substances inhibit e.g. *Aspergillus niger*, *T. rubrum*, *C. albicans* and control e.g. *Puccinia recondita*, *Erysiphe graminis*, *Gliocladium virens*, *Fusarium moniliforme* on tomato, *Pyricularia oryzae* on rice and *Rhizoctonia solani*.

From these series, compound **7.07**, F-155 [149508-90-7; (R)-, 16815-38-2; (S)-, 168125-52-8] has been claimed to protect wheat seed from fungal attack in the presence of Rose Bengal.[7.041]



Many synergistic mixtures have been claimed with F-155. Some hydroxy- and thioalkylazoles (section 3.2) have been transformed into silyl ethers to yield substances such as **7.08**. [7.022, 7.042, 7.043, 7.044, 7.045, 7.046, 7.047]



They inhibit wheat mildew, *Fusarium oxysporum* and *Botrytis cinerea*.

Siloxanes with an additional cyano group show bactericidal, fungicidal, insecticidal, acaricidal and nematocidal activity.[7.048]

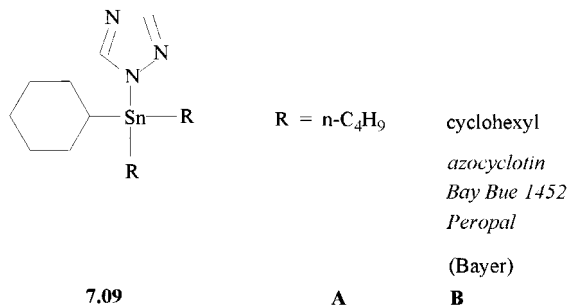
7.3 Azol-1-yl-organogermanium compounds

The germanium analog **7.05B** of flusilazole displays comparable *in vitro* and *in vitro* antimicrobial activities.

In fact, both represent inhibitors of the sterol biosynthesis in *Saccharomycopsis lipolytica* and *Pyricularia oryzae* of similar potency.[7.049]

7.4 Azol-1-yl triorganyl-tin compounds

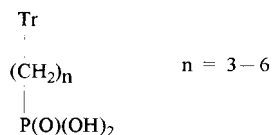
Title compounds **7.09** have been claimed as fungicides which control *Giberella zeae* and *Rhizoctonia solani*.[7.050, 7.051]



Yet, azacyclotin **7.09B** [41083-11-8] has been developed from this series as acaricide against phytophageneous mites.[7.052]

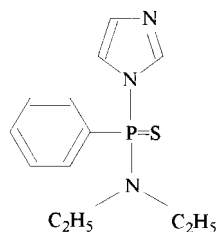
7.5 Azol-1-yl- and (1H-azol-1-yl)alkyl-phosphorus compounds

Title compounds **7.10** have been claimed for their activity as fungicides, e.g. against *Erysiphe graminis* on barley, and as herbicides.[7.053, 7.054]



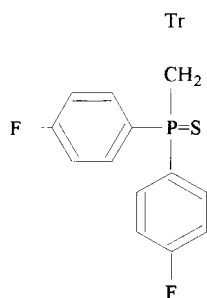
7.10

Imidazolylphosphinamidothionates like **7.11** which control powdery mildew and late blight have been claimed as antifungals.[7.055]



7.11

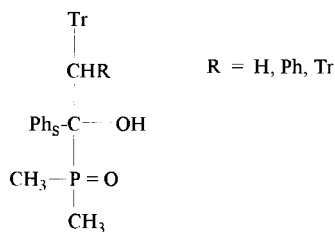
Biscarbylhydriylphosphinyl-1H-azoles have been claimed as fungicides, with **7.12** as the preferred compound.[7.054, 7.056]



7.12

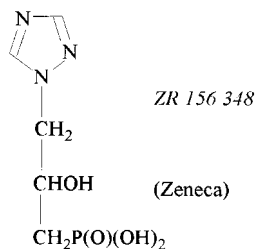
This substance displays interesting activity against *Pyricularia oryzae*, *Rhizoctonia solani*, *Cercospora arachidicola*, *Venturia inaequalis* and in particular *Erysiphe graminis* and *Puccinia graminis*. [7.054]

Substances with an additional hydroxyl like **7.13** inhibit *Erysiphe cichoriacearum* and *E. graminis* sp. *hordei*. [7.057]



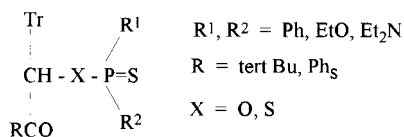
7.13

From a related series, fungicide **7.14**, ZR 156348 has been reported in the ^{14}C -labeled form, and has been developed as a herbicide.[7.058, 7.059]



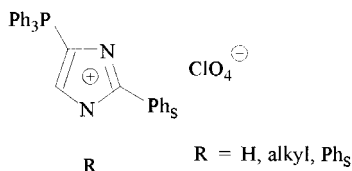
7.14

Phosphonodithioates, phosphoramidothioates and phosphoramidodithioates like **7.15** of imidazolylketones show fungicidal, herbicidal and plant growth-regulating activities.[7.061, 7.062]



7.15

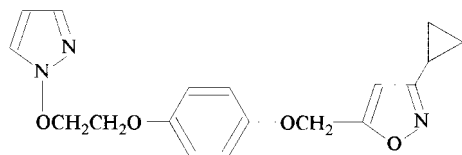
4-Triphenylphosphonium-imidazoles **7.16** display antibacterial and fungicidal activity.[7.060]



7.16

7.6 1-Hydroxy-1H-azoles and their derivatives

The preparation of title imidazole has been disclosed.[7.063] Substances **7.17** have been claimed as fungicides and pesticides.[7.064, 7.065, 7.066, 7.067, 7.068, 7.069, 7.070, 7.071]

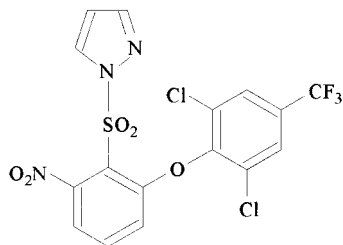


7.17

In **7.17**, pyrazole can be replaced by Tr. They control *Erysiphe graminis* and *Puccinia recondita* on wheat, *Pyricularia oryzae* on rice, and have also been recommended as industrial microbicides.

7.7 1-Arylsulfonyl-1H-azoles

Title substances **7.18** have been disclosed as fungicides, herbicides and plant growth regulators.[7.072]



7.18

Fungicidal compounds **7.19** control *Phytophthora infestans*,[7.073, 7.074]



7.19

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7.7

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9.2 New potential antifungals

3.2.2.11

3.32

$$R = \text{OCH}_2\text{CF}_2\text{CHCF}_2$$

$$-N=Y- = -N=CH$$

TAK-187

(all Takeda)
[3.1088, 1.22]

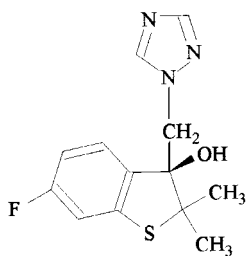
9.01

Tr
-CH₂CH₂-

[1.22]

9.02

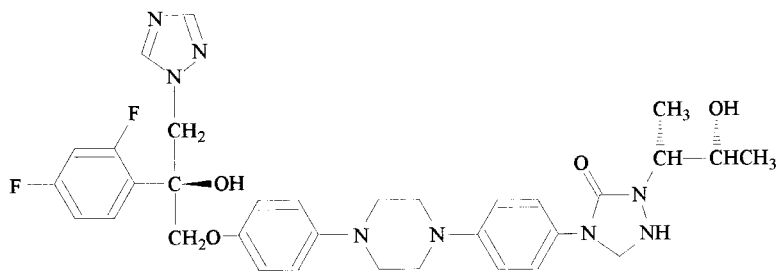
3.2.5



9.03

(Morishita-Roussel)
[1.22]

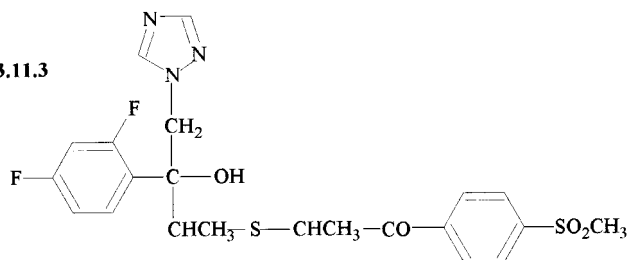
3.11.1



9.04

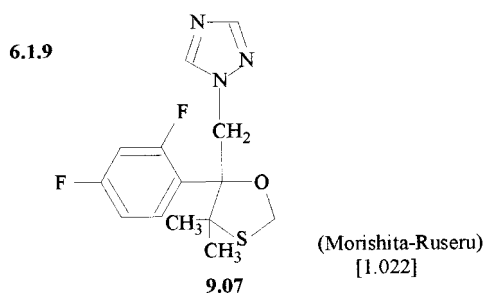
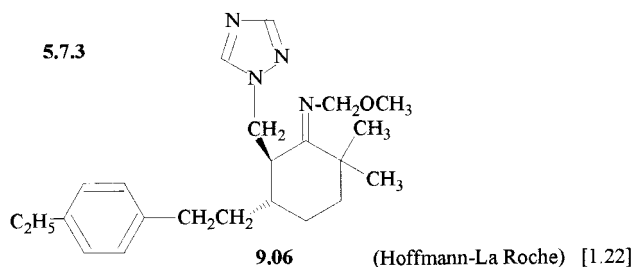
(Schering Corp.) [1.22]

3.11.3



9.05

(Tokyo Tanabe) [1.22]



9.3 Accumulated Chronology and final remarks

Patent applications from section 9.1 amount to 1991 (1), 1992 (0), 1993 (2), 1994 (12), 1995 (23) and 1996 (5). Disregarding data for 1995 and 1996 for incompleteness, the total patent activity on antifungal azoles presented in this book can be grouped in three time periods.

Table 9.1 Patent applications 1980-1994

year span column a	patent applic. b_{10}	patents per year c_{10}	c_{11}/c_{13} , c_{12}/c_{13} d_{10}
a_1 1980-1984	b_{11} 595	c_{11} 119	d_{11} 2.0
a_2 1985-1989	b_{12} 457	c_{12} 91	d_{12} 1.6
a_3 1990-1994	b_{13} 293	c_{13} 58	d_{13} 1.0

After a peak around 1983 for most azole groups (chapters 2 to 5), patent activity has dropped, but still remains one-half (see Table 9.1, column c_{10}). This is rather surprising since the route to a non-toxic antimycotic for long-time therapy has proven to be so much more difficult, and costly, than it was to find a topical antimycotic previously.

The total research activity (patents, papers and books, p+p) is presented in Fig. 9.1 and Table 9.2. Again, the annual numbers may lack precision in the last digit, due to e.g. multiple citation of review articles, or unresolved patent genealogy.

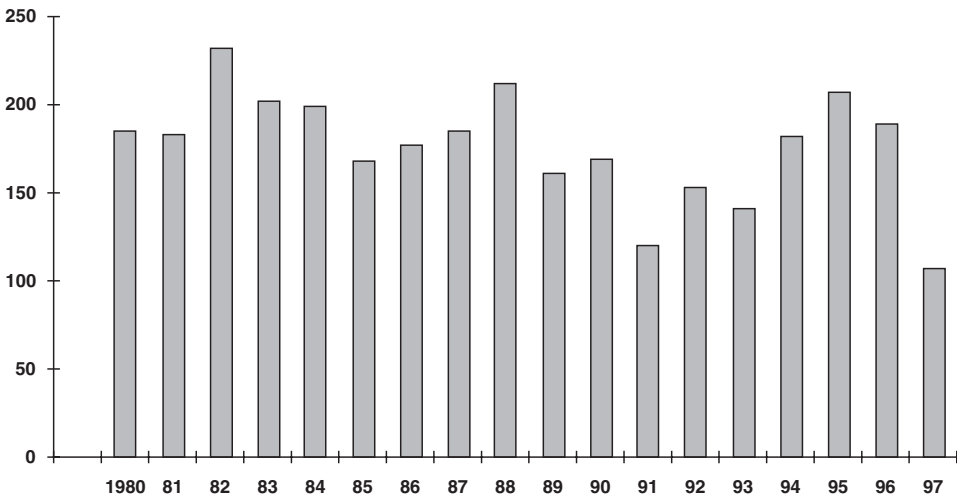


Fig. 9.1 Chronology of 3174 patents and papers (p+p) from 1980 to 30 October 1997, from [1.01] and this book.

Table 9.2 Patent applications + publications (p+p) 1980-1994

year span	p+p	(p+p)/year	$c_{21}/c_{23}, c_{22}/c_{23}$	portion of papers $1 - b_{10}/b_{20}$
column a	b_{20}	c_{20}	d_{20}	e_{20}
a_1 1980-1984	b_{21} 999	c_{21} 200	d_{21} 1.3	e_{21} 0.40
a_2 1985-1989	b_{22} 908	c_{22} 181	d_{22} 1.2	e_{22} 0.50
a_3 1990-1994	b_{23} 765	c_{23} 153	d_{23} 1.0	e_{23} 0.74

Leaving aside incomplete data for 1995-1997 (Fig. 9.1), the three five-year spans present similar trends yet with different rates (columns d_{10} and d_{20}): With time, the total average annual research output p+p (column c_{20}) decreases much slower than that of patents alone (column c_{10}), and the fraction of publications within the sum of patents and papers increases dramatically (column e_{20}) from 40 % to 62 %.

Taking earlier data, [1.01] we arrive at Fig. 9.2 for 30 years of research in anti-fungal azoles.

Even though patent activity has dropped to one half by the last complete five-year period, publication activity has continuously increased. And data of Fig. 9.1 for 1995–1997, though incomplete, allow to anticipate still another rise of total research activity (p+p) on antifungal azoles for 1995 to 1999.

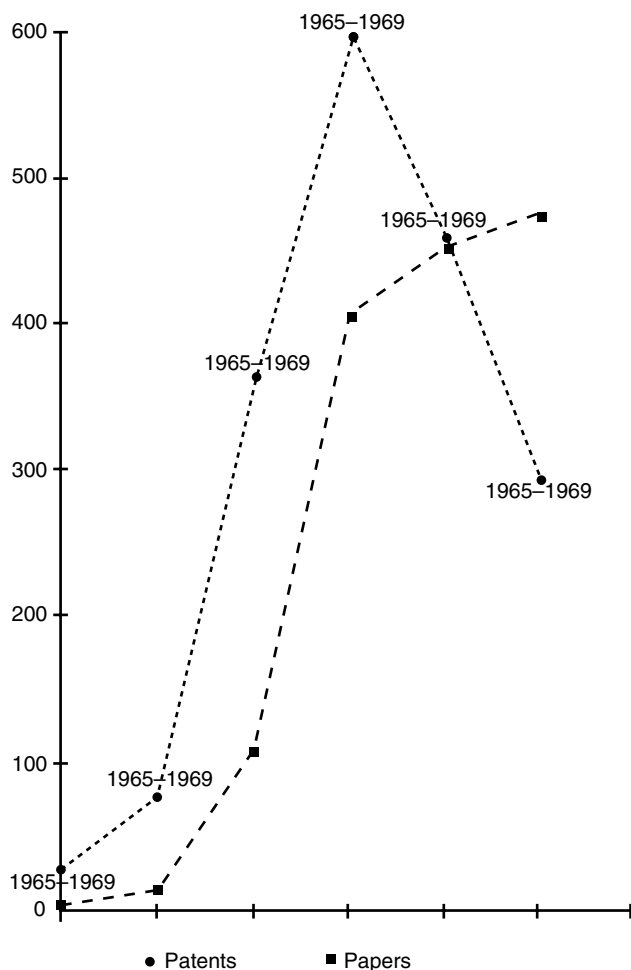


Fig. 9.2 Chronology of patents and papers 1965–1994, from [1.01] and the present book.

These simple statistics reflect, that azole research activity in the last 15 years has shifted from broad structural modification of lead compounds to a deeper investigation of the fungicidal action, the toxicity of antifungals in long-term treatment, and the development of resistant fungal strains.

Aside from azoles, other chemical classes, natural products and peptides, appear promising,[1.23] and yet each new compound will have to outperform the best current azoles. Especially with the grim outlook of AIDS (13% increase of patients per annum, 40 millions infected by the year 2000[1.24]), the deeper understanding gained from 30 years of research in antifungal azoles will be a source of greater information on the chemotherapy of human, animal and plant mycoses regardless into which chemical classes the future will lead.

Index

Introduction

The following terms are considered ubiquitous in this book and are therefore not indexed:

Activity against, antibacterial(s), antifungal(s), antimicrobial(s), antimold, anti-mycotic(s), azole(s), bactericides(s), bacteriostatic(s), biocide(s), fungicide(s), dermatophyte(s), fungistatic(s), fungitoxic, Gram-negative, Gram-positive, imidazole(s), microbicide(s), mycostatic(s), pesticide(s), 1,2,4-triazole(s), yeasts.

Inventing companies are indexed only in connection with individual structures carrying a name or at least a company code. Chemical subgroups (like carbinols, esters, tetrahydrofurans etc.) can be traced through the Contents pages and are as a rule not indexed.

Plant diseases are indexed by causating agent and not by hosts. Excellent Latin/English and English/Latin lists of phytopathogenic fungi and diseases are available.[1.17]

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